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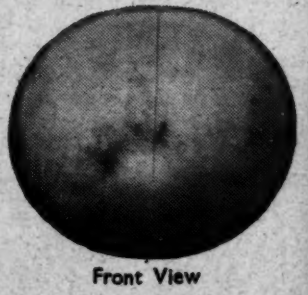

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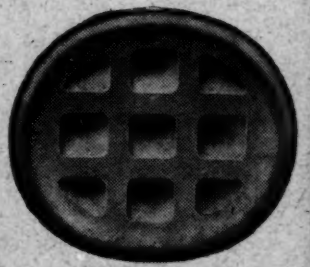

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 25 1952

THE ROLE OF APNOEA IN ANAESTHESIA FOR MAJOR SURGERY

BY

T. CECIL GRAY, M.D., F.F.A.R.C.S., D.A.

AND

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There has been widespread support for the concept which views anaesthesia as a triad (Rees and Gray, 1950), the components of which, narcosis, relaxation, and analgesia, ideally are produced by specific drugs with selective actions. It is now a generally used method of anaesthesia to induce sleep with thiopentone, to produce muscular relaxation with a relaxant drug, and to reduce the response of the patient to noxious stimuli by the use of nitrous oxide and occasionally a more potent specific analgesic drug such as pethidine.

During the past six years an anaesthetic technique based on this principle has been adopted by us. Thiopentone has been used in minimal doses to produce sleep, a 50% mixture of nitrous oxide and oxygen, if necessary supplemented by pethidine (or, in the earlier years, very minimal doses of ether), to produce analgesia, and a paralysant drug to attain relaxation and initiate the control of respiration. As a result of the respiratory depression subsequent upon adequate doses of the relaxant agents, there has been no hesitation in resorting to completely controlled respiration for the cases in which this technique has been employed. The experience gained during this period led to the conclusion that use of controlled respiration reduced the dose of both relaxant and thiopentone which it was necessary to administer in these cases. The examination and significance of this possibility are the subject of this paper.

Effect of Controlled Respiration on Dosage of Relaxant Agent

It must be remembered that the muscles of the abdominal wall vary their tone during respiratory activity (Best and Taylor, 1945; Lovatt Evans, 1952). Relaxation—that is, the reduction of tonus—of these muscles, like any other muscle group, can be achieved either by diminishing the response of the muscle fibres to activity of their motor neurones, as, for example, by giving a relaxant drug, or by reducing the number of stimuli passing down the motor nerve, and this latter effect can be used to intensify the former.

The activity of the respiratory motor nerve is regulated by the respiratory centre, and any factor which either diminishes or increases the activity of this centre will correspondingly diminish or increase the tonus of the abdominal musculature. It is presumed in the argument which follows that there will be no "depression" of the respiratory centre either by anoxia or by anaesthetic drugs.

During controlled respiration two factors result in diminished activity of the respiratory centre: they are (*a*) the rhythmical inflation and deflation of the lungs, and (*b*) the adequate pulmonary ventilation which maintains a normal blood carbon dioxide level.

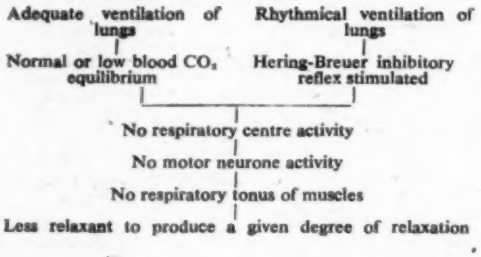
The first of these factors requires little amplification. The establishment of controlled respiration itself tends to prolong the apnoea by overstimulation of the inhibitory Hering–Breuer reflex resulting from the regular cyclical inflation of the lungs (Burstein, 1949). That curarization alone is not responsible for maintaining the apnoea in patients who are anaesthetized by the technique under review is suggested by the fact that they not infrequently move their limbs or the muscles of the face while their respiratory activity is still in abeyance.

The second factor is of the greatest importance. The blood carbon dioxide level plays a dominant part in determining the activity of the respiratory centre, and a consideration of the sequence of events following the administration of a relaxant drug will demonstrate the importance of controlled respiration. The paresis of the muscles of respiration which is an inevitable consequence of injecting any relaxant agent results in a diminished minute-volume of respiration, which in turn is followed by a raised blood concentration of carbon dioxide, because equilibrium between blood carbon dioxide production and excretion takes place at a higher level. Dosage with a relaxant drug therefore produces a state in which the activity of the respiratory motor neurones is increased although the response of the muscles to this activity will be decreased. In other words, a higher dosage of relaxant will be required to produce flaccidity of the muscles. There is here a vicious circle, which can be broken by either "controlled" or "assisted" respiration.

The necessity for assistance of respiration in the curarized patient is universally recognized, but there has been a tendency to regard the persistence of some spon-

taneous respiratory activity as preferable in all cases where there is not an absolute surgical indication for full control of the respiration (as, for example, in open chest surgery). A state of "assisted" respiration in which the blood carbon dioxide level is maintained within normal limits, even if desirable, would seem technically difficult to attain. Even then, however, such a patient, by virtue of the activity of these muscles and the consequent maintenance of tonus, will require more relaxant than the patient in complete respiratory arrest. The probability that this is a valid conclusion is borne out by Dundee (1952).

A patient, therefore, who is in apnoea and whose respiration is adequately controlled will require less relaxant than a patient with spontaneous respiratory activity, because of the following train of events:


Adequate ventilation of lungs
Rhythmical ventilation of lungs
Normal or low blood CO_2 equilibrium
Hering-Breuer inhibitory reflex stimulated
No respiratory centre activity
No motor neurone activity
No respiratory tonus of muscles
Less relaxant to produce a given degree of relaxation

Effect of Controlled Respiration on the "Sleep" Dose of Intravenous Barbiturate

From the earliest days of the use of relaxants there was a strong clinical impression that the dose of thiopentone required to maintain sleep was smaller in patients whose respiration was controlled than in those whose respiration was spontaneous or assisted. It was suggested that this might in some part be due to pharmacological potentiation of thiopentone by D-tubocurarine chloride (Gray and Halton, 1946). A controlled investigation, however, on human volunteers led to the conclusion that there was in fact no such potentiation when the respiration was not controlled (Gray, Gregory, Rees, and Fenton, 1951). Dundee (1952) has (*a*) established that there is a statistically significant reduction in the dose of thiopentone required by patients whose respiration is controlled, and (*b*) investigated and indicated the possible factors, other than those suggested by Brennan (1952), responsible for this finding.

Discussion

There are few who would question the desirability of producing maximal effects from minimal doses of relaxant in order to ensure at the end of an operation more complete elimination and ready reversal by antidotes. The maintenance of apnoea during anaesthesia by controlling the respiration contributes towards this end by obtaining the greatest degree of muscular relaxation from a given dose of relaxant. Furthermore, such control of the respiration results in a quieter field of operation, for which the surgeons are undoubtedly grateful.

It is well established that the anaesthetic agents are directly depressant to the myocardium and have, in addition, varying degrees of effect on cardiac rhythmicity and vasomotor control. In addition to these disturbances of the circulation they may impair the function of various parenchymatous organs. The desirability of reducing the dosage of these drugs in clinical practice must be undisputed.

In view of the considerations outlined above it is suggested that apnoea, with controlled respiration, is a valuable means of achieving this and should therefore be looked upon as an integral feature of the technique for anaesthesia in major surgery and not as something to be avoided if possible, or regarded as a nuisance if inevitable.

There is an additional advantage to be gained from controlling the respiration. Breathing into anaesthetic apparatus inevitably places some additional strain upon the patient, although with well-designed anaesthetic machines this may be minimal. Nevertheless it would seem better that this extra energy should be expended by the anaesthetist rather than by the patient, and, as Waters (1942) pointed out, it may be "desirable to relieve a weak patient from the energy output necessary to contract the diaphragm and intercostal muscles."

An objection to the use of controlled respiration for all major surgery which must be considered is the possibility that the efficiency of cardiac filling is impaired by the intermittent positive pressure and that as a result the cardiac output will fall and the circulatory condition deteriorate. It has been shown that the cardiac output depends upon the average intrathoracic pressure, and there is no doubt that certain types of intermittent positive-pressure respiration produce circulatory depression. However, if the pressure at which the lungs are ventilated is applied according to a curve which shows a slow rise to a maximum during inspiration, followed by a rapid expiratory fall to zero pressure and then a pause at least as long as the period of inflation before the next cycle begins, the rise in mean intrathoracic pressure is small and the cardiac output unaffected (Cournand *et al.*, 1948). The knowledge and application of this correct type of intermittent pulmonary inflation are extremely important and an integral part of the technique which is advocated. Moreover, any machine which may be used to maintain artificial pulmonary ventilation must be capable of giving the correct type of respiratory pressure curve (Esplen, 1952a, 1952b; Musgrove, 1952).

Conclusion

In the light of these considerations we suggest that apnoea should be regarded as an essential component of the syndrome which we induce in our patients in order to prepare them for, and to protect them from, surgery. The time has come, in our opinion, to substitute for the triad principle of anaesthesia outlined at the beginning of this paper a tetrad which can be regarded as a pyramid which has as a base apnoea, upon which are constructed the sides of the pyramid—narcosis, relaxation, and analgesia.

Summary

This paper discusses the effects of "controlled respiration" on the dosage of relaxant drug and thiopentone found to be necessary during anaesthesia. As in both cases smaller doses are used in patients whose respiration is controlled than in those in whom there is spontaneous respiration, it is suggested that "apnoea" should be regarded as an important feature of the technique of anaesthesia for any major surgery.

The importance is emphasized of maintaining the correct type of pressure curve of inflation and deflation during controlled respiration.

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INFLUENCE OF CONTROLLED RESPIRATION ON DOSAGE OF THIOPENTONE AND D-TUBOCURARINE CHLORIDE REQUIRED FOR ABDOMINAL SURGERY

BY

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In using the anaesthetic sequence D-tubocurarine chloride/thiopentone/nitrous oxide/oxygen, an impression was formed that smaller doses of barbiturate were required when the patient was rendered apnoeic and respiration was manually controlled than when the respiratory excursion was only aided or spontaneous respiration was thought sufficient to ensure full oxygenation (Gray and Rees, 1952). Thiopentone and D-tubocurarine chloride being drugs whose dosage can be accurately measured, it was decided to find out whether manual control of respiration actually does reduce the amount of thiopentone required to produce narcosis.

Experimental Procedure

The average requirements of thiopentone and D-tubocurarine chloride for two comparable series, each of 100 cases (for abdominal surgery), were noted. No patient was included in either series in whom any factor was present which might influence the dose of barbiturate or relaxant required to produce narcosis. These factors included liver dysfunction (Dundee, 1952a), raised blood urea (Richards, Kueter, and Taylor, 1950), severe anaemia (Dundee, 1952b), or acquired tolerance to analgesic or sedative drugs (Dundee and Gray, 1951). Cases in which severe blood loss occurred during operation were also excluded.

All subjects were anaesthetized by the technique recommended by Gray (1948), save that the drugs used were limited to thiopentone, D-tubocurarine chloride, and 50% nitrous oxide and oxygen. In one series of cases apnoea was produced following induction of anaesthesia, and respiration was manually controlled throughout the operation. Spontaneous respiration was allowed to persist, or respiration was aided periodically in the second series of subjects. Premedication was the same for all patients—morphine 1/6 gr. (10 mg.), with atropine 1/100 gr. (0.65 mg.), given 45–60 minutes before induction of anaesthesia. Once anaesthesia was induced, supplementary doses of barbiturate and relaxant were given in amounts not exceeding 50 mg. and 3 mg. respectively, so that at no time did the dose administered to the patient exceed the requirements by more than these amounts. The series were limited to operations lasting two hours or over. Most patients were anaesthetized personally, and for the remainder, so far as was possible, the same anaesthetist was employed for an equal number of cases from each series. The cases were further balanced so that approximately equal numbers of operations in each series were performed by the same surgeons in the same hospitals.

TABLE I.—*Showing Details of the Two Series of 100 Cases*

	Aided or Spontaneous Respiration	Manually Controlled Respiration
Average age	48·4 years	46·9 years
Number of Males	59	70
Number of Females	41	30
Operations:		
Gastrectomy	65	65
Operation on bile ducts	10	10
Hysterectomy	6	6
Incisional hernia	6	5
Entero-anastomosis	5	5
Lumbar sympathectomy	4	4
Bilateral inguinal hernia	3	4
Colectomy	1	1

The weight of all patients was noted before operation and the total amount of drugs administered was recorded in mg./kg. every 15 minutes for two hours. Details of the patients and the operations performed in each series are given in Table I. It will be seen that two series of cases were obtained whose requirements of thiopentone and D-tubocurarine chloride were directly comparable.

Results

Table II shows the result of this investigation, which is represented graphically in Fig. 1. These show that subjects

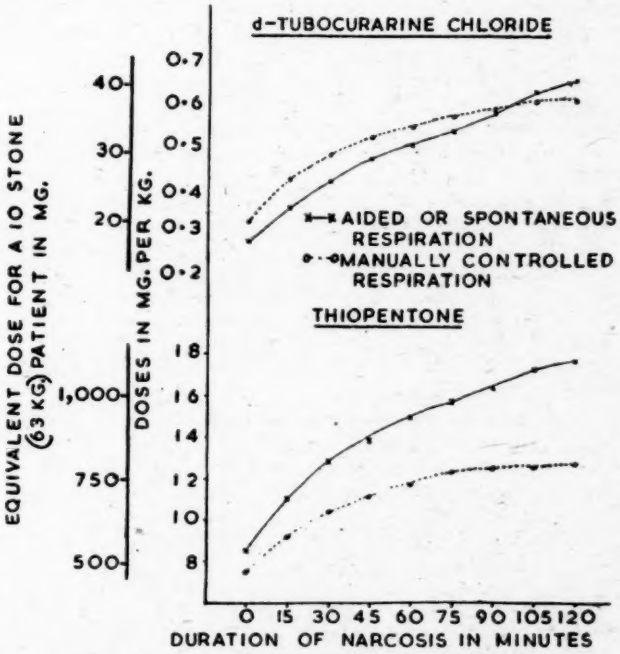

FIG. 1.—Diagrammatic representation of Table II.

in whom respiration is manually controlled during operation require on the average appreciably less thiopentone than subjects in whom aided or spontaneous respiration is employed. The difference in average amounts of thiopentone administered was found to be statistically significant at 60 minutes (S.E. of difference=0.224), 90 minutes (S.E. of difference=0.314), and at two hours (S.E. of difference=0.381). The potentiation of action of thiopentone that occurs during manually controlled respiration becomes more pronounced as duration of operation proceeds. One feels that if it had been possible to obtain a series of cases in which the operations lasted three to four hours the subjects whose respiration was manually controlled may have required only about half the amount of barbiturate administered to subjects with aided or spontaneous respiration.

The picture obtained with D-tubocurarine chloride is rather different. Despite the fact that this substance in no way potentiates the action of thiopentone (Paulson, Lundy, and Essex, 1949; Gray *et al.*, 1951), it might be argued that the administration of large doses of relaxant will decrease the dose of thiopentone required to produce good operating

TABLE II.—*Average Doses of Thiopentone and* D-*tubocurarine Chloride Required at 15-minute Intervals for two Series of Patients Anaesthetized with Thiopentone/*D-*tubocurarine Chloride/Nitrous Oxide/Oxygen*

Time	Thiopentone				D-Tubocurarine Chloride			
	(*a*) Aided or Spontaneous Respiration		(*b*) Manually Controlled Respiration		(*a*) Aided or Spontaneous Respiration		(*b*) Manually Controlled Respiration	
	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.	mg./kg.	Equivalent for 10-stone Subject mg.
Induction	8·51	536·4	7·54	473·2	0·269	16·91	0·316	19·92
15 min. anaesthesia	11·01	693·8	9·16	577·0	0·352	22·19	0·417	26·29
30 ,, ,,	12·79	806·1	10·44	657·8	0·413	26·04	0·478	30·13
45 ,, ,,	13·79	868·7	11·10	694·1	0·468	29·48	0·521	32·80
60 ,, ,,	14·93±0·20	940·6	11·73±0·10	739·0	0·500±0·013	31·47	0·546±0·013	34·42
75 ,, ,,	15·66	986·7	12·28	773·5	0·533	33·60	0·573	36·11
90 ,, ,,	16·35±0·29	1,029·9	12·46±0·15	785·1	0·579±0·017	36·47	0·596±0·013	37·19
105 ,, ,,	17·20	1,083·9	12·52	788·8	0·631	39·74	0·602	37·91
120 ,, ,,	17·61±0·36	1,109·6	12·81±0·13	806·4	0·657±0·012	41·42	0·605±0·014	38·13

(*a*) 100 subjects with spontaneous or aided respiration. (*b*) 100 subjects in whom respiration was controlled throughout the operation.

conditions. For this reason an attempt was made to administer approximately the same doses of D-tubocurarine chloride to the cases in each series. In order to produce apnoea at the beginning of the operation the dose of D-tubocurarine chloride administered to the subjects with aided or spontaneous respiration during the first 45–60 minutes of anaesthesia was found to be significantly greater than that administered to subjects with aided or spontaneous respiration (S.E. of difference at 60 minutes= 0.0161). However, after two hours' anaesthesia the position was reversed, and subjects whose respiration was controlled now required significantly less D-tubocurarine chloride than their counterparts whose respiration was spontaneous or aided (S.E. of difference=0.0161). An impression was formed that, had an attempt not been made to administer approximately equal amounts of relaxant to both series of cases, this difference would have been more marked. As with thiopentone, it would appear from Fig. 1 that in operations lasting three to four hours the amount of relaxant required when respiration was manually controlled would be very much less than when respiration was periodically aided or spontaneous.

Since the only difference between these two series of cases is the respiratory excursions, it should be possible to relate the differences between manually controlled and aided or spontaneous respiration to the differences in average requirements of thiopentone recorded in Table II. When thiopentone and a relaxant drug are administered and little attempt is made to compensate for respiratory depression, an accumulation of carbon dioxide is inevitable, and if prolonged will result in a decrease in the *p*H of the blood. Studies on diffusion respiration in dogs (Whitehead *et al.*, 1949) show that, although adequate oxygenation can be maintained for long periods with little or no respiratory movement, this is not accompanied by a corresponding removal of alveolar carbon dioxide. These authors have recorded rises in CO_2 content of arterial blood from 36 vols.% to 75 vols.%, and a fall in arterial blood *p*H from 7.45 to 6.72 over 45 minutes, during which time arterial oxygen content was barely altered. Provided manually controlled respiration approximates to the patient's normal respiratory excursions, and CO_2 absorption is efficient, the *p*H of blood in subjects in whom this was performed should remain unchanged throughout the operation. During thiopentone narcosis the amount of drug distributed between plasma and body fat varies with the *p*H of the blood (Brodie *et al.*, 1950). Decreasing the *p*H to 6.8 (by inhalation of CO_2) results in a fall in the blood thiopentone level of about 40%. When CO_2 inhalation was stopped the *p*H rose rapidly to its normal level and was accompanied by a rise in the plasma content of thiopentone.

Changes in Blood *p*H During Operation

The changes in blood *p*H which occurred during manually controlled and aided or spontaneous respiration were investigated, using a Muirhead glass electrode battery-operated *p*H meter. The findings in 25 cases from each series are shown in Fig. 2. For the sake of simplicity actual figures are not given, but changes from the pre-operative *p*H of the blood are shown. There is a wide scatter of the readings from each series, due to variations in the respiratory excursions and the efficiency of the soda-lime, but both series of cases show the same tendency. Fig. 2 confirms that a fall in blood *p*H occurs with aided or spontaneous respiration, but unexpectedly reveals an equally great rise

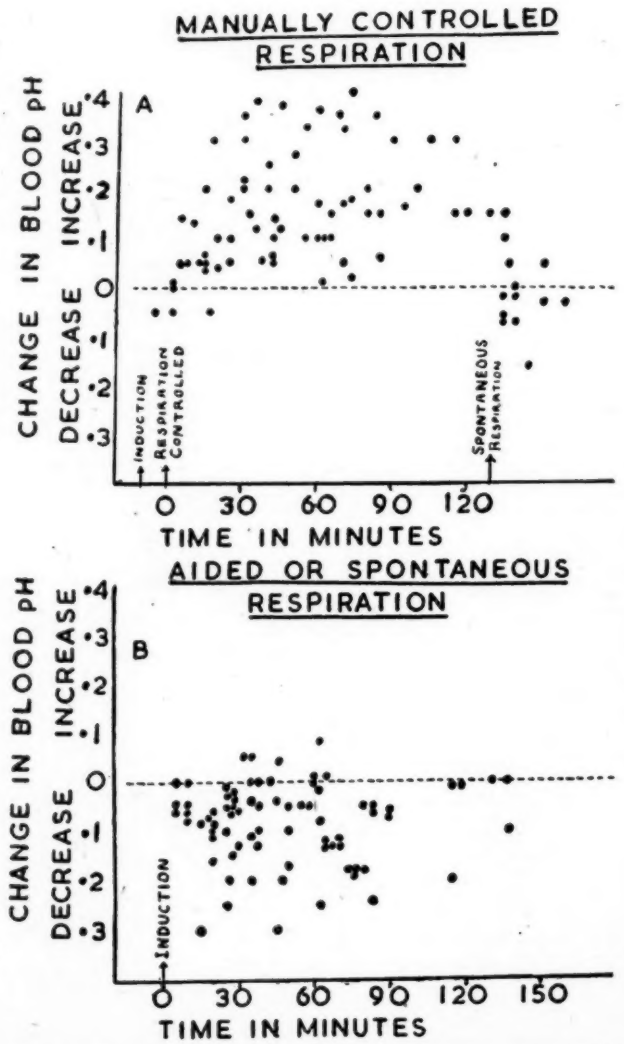

FIG. 2.—Changes in *p*H recorded during operation on 25 of each of the two series of subjects referred to in Table I. Changes in *p*H are recorded as deviations from the pre-operative level.

in *p*H with manually controlled respiration, indicating hyperventilation in the latter series of cases.

During anaesthesia with thiopentone in man, when adequate ventilation is maintained, the variations in *p*H (between 7.34 and 7.56) are not enough to affect the plasma concentration of thiopentone (Brodie *et al.*, 1950). In the two series of cases under discussion the average differences resulting from the two types of respiration are much greater—approximately 0.4. From this one would expect that, for equal doses of thiopentone, plasma levels of the drug would be much higher during manually controlled respiration than during aided or spontaneous respiration (Brodie, 1952, personal communication). The concentration of thiopentone in the cerebrospinal fluid (and hence brain concentration) runs parallel to the plasma concentration (Hubbard and Goldbaum, 1950). From this it follows that the duration of narcosis with a fixed dose of thiopentone would be longer with manually controlled respiration than with aided or spontaneous respiration. This is in agreement with the findings of Table II and Fig. 1.

Further Evidence for Potentiation Effect of "Controlled Respiration"

Confirmatory evidence for this was obtained in investigating the effect of hyperventilation with oxygen on the time taken for various subjects to react to a constant stimulus. The investigation was carried out on fit male patients aged between 31 and 49 years, and the constant stimulus employed was the passage of a cystoscope. Selection of subjects and premedication were the same as for the previous two series of cases. Anaesthesia was induced with doses of thiopentone varying between 450 and 700 mg., injected at a fixed rate of 100 mg. in five seconds. In alternate patients a face-mask was applied immediately consciousness was lost, and hyperventilation was carried out with large flows of oxygen (8–10 litres per minute). This proved impossible in some subjects because of difficulty in obtaining an air-tight fit of the face-mask or because of the gases blowing up the stomach. As a result, only 37 out of 102 patients were hyperventilated; the other 65 were allowed to breathe normally.

Cystoscopy was performed immediately the patient was asleep, and the first reaction to this stimulus was taken as the end-point. Duration of narcosis was thus measured from the end of the injection of thiopentone to the first movement of the patient.

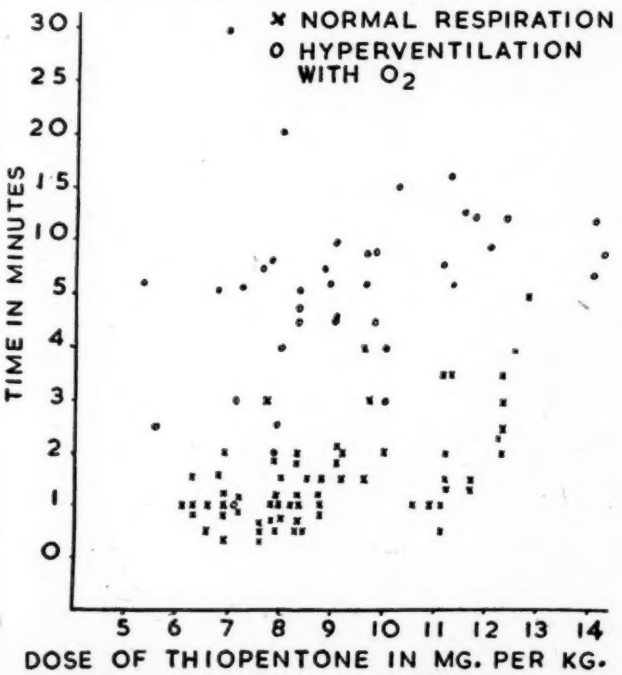

FIG. 3.—Scatter diagram showing times taken for 102 male subjects to react to the stimulus of a cystoscope following varying doses of thiopentone.

Fig. 3 shows the duration of narcosis in subjects who were allowed to breathe spontaneously and in those hyperventilated with oxygen plotted against the dose of thiopentone administered in mg./kg. No direct relation between the dose of thiopentone and the duration of narcosis could be demonstrated in either series, presumably because of acute tolerance to the drug (Mark *et al.*, 1949). However, the results clearly demonstrate a much more prolonged narcosis in subjects who were hyperventilated with oxygen than in those allowed to breathe spontaneously. For the sake of completeness, changes in blood *p*H were measured in a few cases from each series (Fig. 4), and these show the same picture as Fig. 2.

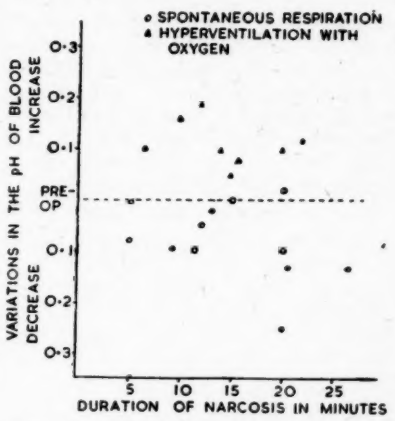

FIG. 4.—*p*H changes recorded during cystoscopy in 18 of the cases referred to in Fig. 3.

Discussion

From these investigations it can be concluded that a moderate degree of hyperventilation, such as occurs in manually controlled respiration, results in a prolongation of the action of thiopentone. While the most likely explanation of this phenomenon is the effect of the altered *p*H of the plasma on the distribution of thiopentone in the body, one cannot be dogmatic and assume that is the sole explanation.

Overventilation for any length of time is accompanied by oliguria and decreased urea clearance (Smith, 1951). In one recorded case of acapnia following hyperventilation the rate of urea clearance was reduced to one-fifteenth of normal (McCance, 1935). It is known that the presence of a high blood urea prolongs thiopentone narcosis (Richards *et al.*, 1950). The possibility exists that during prolonged manually controlled respiration a sufficient rise in blood urea may occur to potentiate the action of the thiopentone and thus reduce the amount of barbiturate required to produce anaesthesia. This possibility was investigated, and

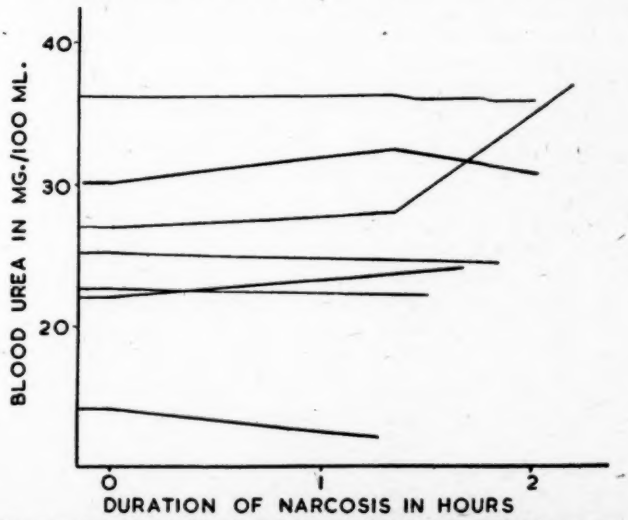

FIG. 5.—Changes in blood urea recorded during operation in seven cases with manually controlled respiration.

Fig. 5 shows actual changes in blood urea recorded during thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen anaesthesia with manually controlled respiration. It can be seen from the results of seven cases investigated that the degree of hyperventilation that occurs during manually controlled respiration has a negligible effect on the blood urea, and in only one case was there any possibility of urea being incriminated as a cause of potentiation of thiopentone. It is interesting to note that in the one case in which a rise in urea was noted an excessive degree of hyperventilation was produced for investigational purposes. It would seem that with controlled respiration as carried out during anaesthesia there are no deleterious effects on kidney function and no marked rise in blood urea.

Loss of consciousness can follow hyperventilation if this is carried to extremes (McCance, 1935; Seevers *et al.*, 1939). A diminution in cerebral blood flow of the order of 30% (part of a general peripheral vasoconstriction) with an average increase of 15% in cerebral oxygen consumption has been reported (Kety and Schmidt, 1946). These would lead to a certain degree of cerebral anoxia, which may be aggravated by the effects of lowering the CO_2 tension on the oxygen dissociation curve of blood. While more oxygen can be taken up by the blood in the lungs, less will be given off to the tissues (Barach *et al.*, 1947). While it is known that potentiation of barbiturate anaesthesia can be accomplished by any means whereby central anoxia is produced (Peterson, Shideman, and Linares, 1950), this could not have played a part in the potentiation of thiopentone observed during manually controlled respiration. In these cases the degree of hyperventilation was so slight that none of the anaesthetists concerned realized that they were in fact hyperventilating the patients until they were told of the *p*H changes of the blood. Furthermore, using the thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen sequence with manually controlled respiration of the same degree as in the series of cases referred to earlier, Prime and Gray (1952) found peripheral vasodilatation rather than vasoconstriction.

The fact that a patient is not breathing spontaneously will reduce the tone of the intercostals and hence abdominal muscles. If thiopentone/nitrous oxide/oxygen were used without a muscle relaxant, controlled respiration would reduce the amount of barbiturate required to produce satisfactory relaxation. This does not apply directly to the cases described above, but is the probable explanation of the lowered requirements of D-tubocurarine chloride observed at the end of two hours' anaesthesia with manually controlled respiration, as compared with patients who were allowed to breathe spontaneously.

All of the arguments quoted above are applicable to the anaesthetic technique described by Brennan (1952). With doses of 500 mg. of thiopentone for a large healthy adult he was able to produce long periods of narcosis. Undoubtedly he used a higher percentage of nitrous oxide (75%) to obtain a better analgesia, but it is doubtful if this actually resulted (Seevers *et al.*, 1937). Hyperventilation was purposely carried out from the beginning of the operation, and the changes in *p*H of the blood must have been greater than those recorded in either Fig. 2 or Fig. 4.

Conclusions

1. Subjects anaesthetized with thiopentone/D-tubocurarine chloride/nitrous oxide/oxygen require appreciably smaller amounts of barbiturate when respiration is manually controlled than subjects in whom respiration is aided or spontaneous.

2. More D-tubocurarine chloride is required for the first 45–60 minutes of the operation when respiration is controlled, but after two hours of anaesthesia requirements of relaxant are less than for subjects whose respiration is spontaneous or periodically aided.

3. With this sequence of drugs, aided or spontaneous respiration is accompanied by a fall in the *p*H of the blood. Manually controlled respiration results in a rise in blood *p*H, indicating some degree of hyperventilation.

4. The changes in the *p*H of the blood, by affecting the distribution of thiopentone in the body, could account for conclusion 1.

5. Hyperventilation with oxygen prolongs the duration of thiopentone narcosis.

6. Other effects of hyperventilation which have been discussed are unlikely to have any potentiating effect on thiopentone.

I am grateful to Professor C. A. Wells and other members of the staff of the Professorial Surgical Unit of Liverpool Royal Infirmary for providing cases and co-operating in this investigation. My thanks are also due to Miss G. C. Jones for her help in the biochemical investigations.

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A NEW ARTIFICIAL RESPIRATOR

BY

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The increasing use of anaesthetic methods which involve complex intravenous techniques and the deliberate production of a state of apnoea have led to an interest in machines which are capable of ventilating a patient's lungs automatically and so restoring to the anaesthetist the freedom of his hands.

The respirator here described (Fig. 1) was designed for patients anaesthetized for thoracic surgery, and was first subjected to clinical trial at Aintree Hospital, Liverpool, in September, 1949. Since its introduction it has maintained respiration throughout the course of 538 major thoracic operations, of which 432 were cases of lung resection. That the trial has extended into what is, for this type of surgery, a long series of cases, speaks for the acceptance of the machine by surgeon and anaesthetist, and for the absence of complications that could be attributed to its use.

The respirator is of simple construction, the original model being built without special tools in a home workshop. Essentially the mechanism consists of:

1. A three-way tap by means of which the anaesthetic circuit can be connected to a hand-operated breathing-bag, or to a bag inside a glass bottle, at will.

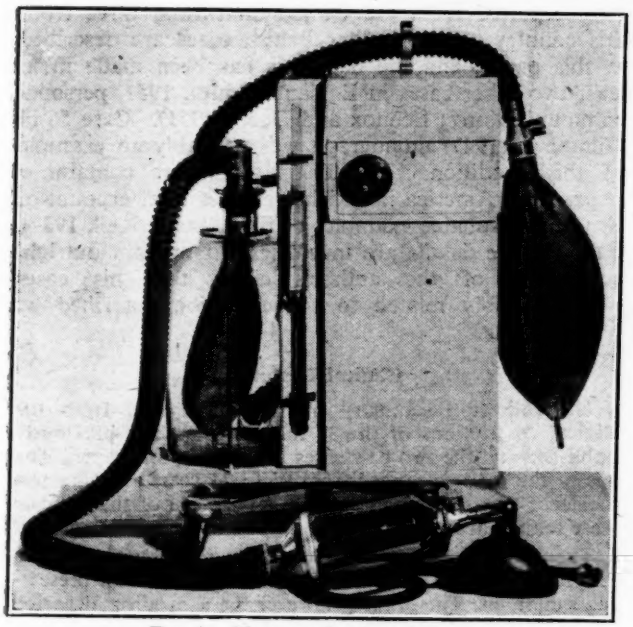

FIG. 1.—Photograph of respirator.

2. A magnetically controlled valve which utilizes a flow of compressed air to build up and disperse an air pressure within the bottle, the alternating pressure cycle rhythmically compressing and releasing the breathing-bag and inflating and deflating the lungs. During deflation the compressed-air stream is used to create a venturi effect within the valve, the negative pressure produced being sufficient to overcome the inertia and resistances of the gas system and assist the pressure in the breathing-bag to return to the atmospheric level.

3. A device which enables the capacity of the system to be altered and permits the frequency of the respiratory cycle to be varied.

4. A self-regulating expiratory valve which allows any excess of anaesthetic gas to escape and ensures that the breathing-bag contains a constant volume of gas at the end of each expiration.

Provision is also made for varying the relative lengths of the inflationary and expiratory phases and for the retention of a positive pressure in the lungs throughout expiration if desired. Fig. 2 is a reproduction of one type of

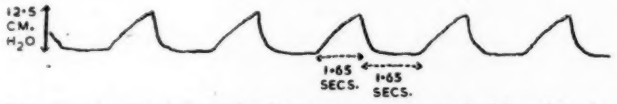

FIG. 2.—A type of tracheal-pressure curve attainable with the machine.

tracheal-pressure curve which is attainable by ventilation with the machine. This follows closely the ideal form of curve described by Cournand *et al.* (1948). Should spontaneous respiration occur, the design of the valve makes it possible for the machine to respond to the resultant pressure changes and so follow the patient's respiratory pattern.

The rate of respiration may be adjusted within a range of 8 to 30 respirations a minute, and the pressure range available is from 5 to 25 cm. of water.

The water manometer used to record the pressure changes in the anaesthetic circuit also serves as a safety valve, the length of its tube limiting the inflation pressure that the machine can apply to 30 cm. of water. It is cut out of circuit when the three-way tap is turned to connect the patient to the hand-operated breathing-bag.

Features of the machine in use include simplicity of operation, a satisfactory performance at low inflation pressures, the assistance given to deflation, and a "chattering" or increase in rate which gives audible warning (when the mechanism is suitably set) should an obstruction to respiration develop. The machine has been found to require very little attention in the way of maintenance, and the breathing-bag is easily removed for cleaning purposes.

Fig. 1 shows the appearance of the original apparatus, which is being developed and produced commercially by Medical and Industrial Equipment Ltd., London, under the name of the "Aintree respirator." A more detailed account of the machine may be found elsewhere (Esplen, 1952).

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THROMBOTIC MICROANGIOPATHIC HAEMOLYTIC ANAEMIA (THROMBOTIC MICROANGIOPATHY)

BY

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The condition described in this paper as thrombotic microangiopathy has attracted little attention outside the United States of America, where it is commonly known as thrombotic thrombocytopenic purpura. Clinically, the typical fully developed case presents a syndrome of fever, haemolytic anaemia, purpura, and fluctuating neurological disturbances; when this syndrome is present the diagnosis can be made at the bedside. Often, however, the most characteristic component of the syndrome, the *waxing and waning* neurological signs, appears only in the terminal stages of the illness; even in the earlier stages, however, identification by laboratory studies of the haemolytic nature of the anaemia and of the thrombocytopenia underlying the purpura should enable the diagnosis to be made, for the association of haemolytic anaemia and thrombocytopenic purpura is found in only a few conditions, most of which can be distinguished from thrombotic microangiopathy on other grounds. Unfortunately, the disease is not widely known and it is seldom considered in diagnosis: in most cases the correct diagnosis has first been made *post mortem*, by recognition of the pathognomonic disseminated lesions which occur only in vessels of microscopic calibre. No treatment has yet proved effective, and the disease has been fatal in all the recorded cases, usually within two to six weeks of its clinical onset. There are grounds for hoping that earlier diagnosis and treatment may lower the mortality. The following account of thrombotic microangiopathy is therefore presented, with a report of two new cases.

Historical

The first account of an undoubted example of this disease appears to have been given by Moschcowitz (1924, 1925), who described a case of acute febrile haemolytic anaemia with petechiae and the development of neurological signs shortly before death; Libman is said to have recognized the condition clinically as a "new" disease. Histological examination *post mortem* showed hyaline thrombosis of terminal arterioles and capillaries. Moschcowitz recognized that the wide dissemination of these lesions was unique; he thought that

the thrombi were formed of agglutinated erythrocytes and that the disease was caused by some powerful haemagglutinative and haemolytic poison. He mentioned that Lederer had seen four cases "clinically identical" with his case but recovering after a blood transfusion (Moschcowitz, 1925); unfortunately, this comment has led to misquotation of Moschcowitz's case as a fatal case of Lederer's anaemia and so to the erroneous statement that disseminated hyaline vasothrombosis is a characteristic of the latter (O'Donoghue and Witts, 1932; Whitby and Britton, 1950).

No further case was described until Baehr *et al.* (1936) published a composite clinico-pathological study of four cases. They believed that the thrombi were composed of blood platelets, and that the associated thrombocytopenia was due to the available supply of platelets being used up in the formation of the countless lesions. One of their cases was also reported by Friedberg and Gross (1936); another was redescribed by Gitlow and Goldmark (1939–40). Since then only 25 unequivocal cases have been reported (Altschule, 1942; Bernheim, 1943; Trobaugh *et al.*, 1946; Carter, 1947; Engel *et al.*, 1947; Fitzgerald *et al.*, 1947—3 cases; Singer *et al.*, 1947; Muirhead *et al.*, 1948; Green and Rosenthal, 1949—2 cases; Gore, 1950—5 cases; Singer *et al.*, 1950; Wyatt and Lee, 1950; Goldenberg *et al.*, 1950; Clinicopathologic Conference, 1950; Meacham *et al.*, 1950, 1951—2 cases; Symmers and Barrowcliff, 1951; Rackow *et al.*, 1952), making a total of 30 cases, to which Case 4* in Pagel's (1949) paper on acronecrosis can be added.

The complicated case described by Norman, Brown, and Spitz (Clinicopathologic Conference, 1946) was possibly fundamentally of the same nature; unfortunately, the histological description is sketchy and there are no illustrations. Four other supposed cases have been published. One was attributed by Ehrich and Seifter (1949) to iodine intoxication; in the absence of adequate data the accuracy of their diagnosis is questionable. The Italian case of Vannucchi and Esente (1949) cannot be accepted as proved, as there was no histological study; the equivocal clinical and atypical haematological findings do not support the diagnosis, and the ophthalmoscopic observation of thrombosis of major retinal veins is contrary to the findings in every other recorded case, in which only vessels of microscopic dimensions have been affected. The clinical and pathological descriptions and the illustrations of Wallace's (1951) two Australian cases are not convincing.

Although only 36 cases or supposed cases have been reported, thrombotic microangiopathy is probably not as rare as this number might suggest. Familiarity with the condition is an unusually important factor in its recognition; no fewer than 17 of the first 25 cases were described by workers in only three centres (Mount Sinai Hospital, New York; Harvard Medical School and the Boston City Hospital; and the Armed Forces Institute of Pathology, Washington). Wider knowledge of its occurrence rather than an increasing incidence of the disease probably accounts for the fact that 23 unequivocal cases were reported in the six years 1946 to 1951, while only seven were recorded in the 20 years from 1924, when Moschcowitz first described the condition. Of the 36 published cases or supposed cases, 30 were reported from the United States and three from this country. Two further British cases are described in this paper, and the diagnosis has been made in at least two other cases in England (Smith, 1951, personal communication†; Lennox and Dacie, 1951). Case 56 in Gilmour's (1947) monograph was probably an example of this condition. The British literature contains a paper from America in which there is a brief account of two other probable examples of this disease (Keil, 1937), although the details are insufficient to warrant outright acceptance of the author's claim that his cases were probably related to the condition described by Moschcowitz.

Clinical Features

The following summary has been prepared from the clinical descriptions of the 31 indisputable cases previously published and the two new cases reported in this paper. The age of the patients ranged from 9½ to 74 years; the greatest incidence was in young adult life. Nineteen of the patients were female and 12 male. Six patients were of Negro race.

The onset of grave illness is usually rapid, with asthenia and haemorrhagic manifestations as the commonest presenting symptoms. There may, however, be a prodromal period of weeks or months of vague ill-health, sometimes with muscle or joint pains or urticaria. Sometimes the acute illness is prefaced by a febrile upper respiratory infection which leaves the patient unexpectedly exhausted, or by gastro-intestinal disturbance and vague abdominal pain. Neurological symptoms or mental confusion may precede other manifestations; one patient (Goldenberg *et al.*, 1950) presented with a severe psychosis which necessitated admission to a mental hospital.

The characteristic clinical features of the established illness are fever, haemolytic anaemia, purpura or other haemorrhages, and fluctuating neurological disturbances.

Fever.—Fever up to 100–102° F. (37.8–38.9° C.) usually occurs; there may be terminal hyperpyrexia.

Haemolytic Anaemia.—Anaemia has been present in every case and is usually severe; it develops rapidly and is usually manifest when the patient first comes under observation. It may precede the haemorrhagic manifestations, and its severity is essentially independent of the latter. Haemolytic jaundice was present in 24 cases.

Haemorrhagic Manifestations.—Haemorrhagic lesions are usually obtrusive and rarely (four cases?) absent; they are commonly present when the patient comes under observation, but may first appear at any time subsequently. Purpura is commonest; only a few easily overlooked petechiae in skin or mucosae may be present, or there may be severe widespread purpura which often develops in crops. The tourniquet test may be positive before there is spontaneous bleeding. There may be haemorrhage from any of the orifices of the body; haematuria was a presenting symptom in five cases.

Neurological Disturbances.—Neurological abnormalities are usual, although they may first appear late in the course of the disease. In a large proportion of cases they have shown a distinctive multiplicity and waxing and waning character. Paraesthesiae, dysphasia and related disorders, cranial nerve lesions, cerebellar signs, isolated paralyses or pareses, monoplegia or hemiplegia, and spasticity are among many recorded transitory manifestations of focal nervous damage. Often, however, the neurological symptomatology is not distinctive (generalized muscular weakness, incontinence, headache, vertigo, delirium, stupor, coma). Convulsions are rare. Electroencephalography showed changes consistent with "diffuse cortical disorder" in one case (Singer *et al.*, 1950) and suggested a cerebral tumour in another (Muirhead *et al.*, 1948).

*I am indebted to Dr. Walter Pagel for allowing me to see sections from this case, which he agrees should be considered an example of thrombotic microangiopathy.

†I am indebted to Professor D. S. Russell, in the absence of Dr. J. F. Smith overseas, for the opportunity to examine the typical histological material from this London Hospital case.

Inconstant clinical findings include moderate enlargement of lymph nodes, spleen, or liver. Uraemia has been observed rarely. Arterial hypertension was recorded in two cases; both were uraemic. The pulse rate is usually proportional to the temperature, but there may be a considerably disproportionate tachycardia. One child showed electrocardiographic evidence of myocardial ischaemia (Engel *et al.*, 1947). Retinal haemorrhages and papilloedema may be present.

Laboratory Findings

Haematology.—Haematological examination typically shows severe haemolytic anaemia, thrombocytopenia, and a leucocytosis which may be leukaemoid. Exceptionally, any of these findings may be absent. The anaemia has commonly been described as normocytic and normochromic; hypochromia, microcytic anisocytosis, and poikilocytosis have been noted in some cases. Although the severity of the haemolytic process varies, erythrocyte counts of two million or less, with a proportional reduction of the haemoglobin level, are common at the first examination. There is usually a pronounced reticulocytosis, and nucleated red cells are commonly found; the number of reticulocytes and nucleated red cells tends to rise during the course of the illness, and counts of the latter have reached figures equivalent to more than 14,000 per c.mm. Erythrocyte fragility in hypotonic saline is normal or slightly increased; Singer *et al.* (1950) noted increased mechanical fragility in one case. Spherocytosis was observed in three cases, in one of which the proportion of spherocytes was noted to increase remarkably as the disease advanced. Sickle cells were not found in any of the Negro patients. The direct Coombs test was negative in the three cases in which it was recorded (Singer *et al.*, 1950; Meacham *et al.*, 1951). Pigment studies usually show hyperbilirubinaemia with an indirect van den Bergh reaction; there is a correspondingly increased excretion of urobilinogen in the faeces and urine.

Leucocytosis with a shift to the left is found in most cases; usually it is of moderate degree, at least in the earlier days, although counts of up to 50,000 have been recorded. Myelocytes, premyelocytes, and myeloblasts may be found in the peripheral blood; the leukaemoid picture was observed in eight cases, in some of which it was transitory. Severe thrombocytopenia is usual and platelets may be practically absent. The thrombocytopenia may be progressive, or successive counts may swing between very low and normal figures; the number of platelets may be above the "critical level" even during an outcrop of purpura. Clotting-time and prothrombin-time are usually normal, whereas bleeding-time is prolonged and clot retraction markedly deficient.

Marrow examination shows normoblastic erythropoietic hyperplasia; myeloid hyperplasia may be associated with an increased proportion of immature cells. Megakaryocytes may be increased in number but are said to show no other abnormality.

Urine.—Protein and excess urobilinogen are usually present. There is no bilirubinuria. Occasional granular casts are often found; erythrocytes are almost always present microscopically and there may be gross haematuria. The urine may be completely normal.

Blood Chemistry.—Hyperbilirubinaemia is the commonest abnormality. Hyperglobulinaemia has been noted in five cases, with a normal or low total protein concentration and an albumin–globulin ratio of approximately unity. Positive cephalin–cholesterol flocculation and thymol turbidity tests have been reported. Non-protein nitrogen is raised in a few cases.

Cerebrospinal Fluid.—The cerebrospinal fluid was normal in nine cases. Six others showed protein concentrations of 40 to 176 mg. per 100 ml., a positive Pandy test, and occasional erythrocytes.

Other Investigations.—Serological tests for syphilis were negative in the 13 cases investigated. Serum agglutination reactions, blood cultures, and other bacteriological investigations have been essentially negative. Occult blood is inconstantly present in the stools.

Diagnosis

Thrombotic microangiopathy was diagnosed *ante mortem* in only three published cases (Engel *et al.*, 1947; Singer *et al.*, 1950; Meacham *et al.*, 1951); there is little doubt that a larger proportion of cases would have been diagnosed during life if the syndrome were more generally known. Indeed, the characteristic diagnostic tetrad of the fully developed syndrome identifies the patient's illness as thrombotic microangiopathy; judging, however, from the available case reports, this tetrad appears to have been complete in considerably fewer than half the published cases. In particular, the characteristically multifarious and fleeting neurological signs usually occur at a late stage, if at all: more commonly, the neurological symptomatology is not diagnostic. Of much greater diagnostic importance is the association of haemorrhagic manifestations and haemolytic anaemia. The frequency of haemorrhage, particularly purpura, as a presenting or early sign of this disease makes it a cardinal diagnostic feature.

As the purpura is practically always accompanied by thrombocytopenia, the differential diagnosis is essentially that of thrombocytopenic purpura in general (Singer *et al.*, 1947; Dameshek, 1947). When the haemolytic nature of the accompanying anaemia is recognized, the number of conditions to be considered in diagnosis is reduced still further, and the correct diagnosis should be attainable in a large proportion of cases. Singer *et al.* (1950) pointed out that thrombocytopenia may be associated with haemolytic anaemia in thrombotic microangiopathy, "idiopathic" acquired haemolytic anaemia, toxic haemolytic anaemia (caused by sulphonamides, etc.), symptomatic haemolytic anaemia (malignant reticuloses, leukaemias, carcinomatosis, etc.), familial haemolytic anaemia in crisis, paroxysmal nocturnal haemoglobinuria, severe liver disease, and untreated pernicious anaemia. Of these, only the "idiopathic," toxic, and symptomatic acquired haemolytic anaemias cannot readily be differentiated by clinical and laboratory study from thrombotic microangiopathy; the leukaemoid blood picture of some cases of the latter is particularly likely to lead to confusion with the symptomatic group unless it is transient. Immunological methods may have diagnostic value, as the Coombs test is usually positive in the "idiopathic" and symptomatic haemolytic anaemias (Singer and Motulsky, 1949) and has been negative in the three published cases of thrombotic microangiopathy in which it was performed.

The ultimate proof of the diagnosis is histological. Biopsy was first suggested by Bernheim (1943), yet its value has scarcely been investigated. A few authors recorded failure to find the lesions in biopsies of marrow, although they were recognized in splenectomy specimens by Green and Rosenthal (1949) and Meacham *et al.* (1951). Little is known about the incidence of the typical vascular changes in tissues accessible to biopsy, and appropriate post-mortem studies would be valuable; lesions were numerous in the skin and in the vastus lateralis examined *post mortem* in one case (Smith, 1951, personal communication; see footnote on page 898). I have made the diagnosis in one case on the basis of a positive skin biopsy in association with the typical clinical picture; permission for a necropsy was not obtained.

Electrocardiography and electroencephalography may be of diagnostic value in demonstrating visceral changes.

Prognosis and Treatment

The disease has been fatal in every recorded case. The period between the first symptom of ill-health and death was less than six weeks in two-thirds of the cases, and less than a fortnight in eight cases. The longest durations were 15 weeks, 6 months, 10 months (two cases), and 3½ years. Although transient clinical improvement lasting a few days is common in the early stages, longer remissions have been recorded in only three cases. In the case described by Engel *et al.* (1947) withdrawal of sulphonamide therapy was followed by such marked improvement that the patient was

able to return home; five weeks later she developed a fatal relapse, which was not preceded by further drug therapy; test doses of sulphonamides had been shown to cause a febrile reaction, with tachycardia and leucocytosis but without evidence of haemolysis or haemorrhage. In another case (Symmers and Barrowcliff, 1951) the patient gradually recovered sufficiently to leave hospital, but relapsed a week later. A much more striking remission, with important therapeutic implications, was observed by Meacham *et al.* (1950, 1951); the patient remained in reasonably good health for 28 months after splenectomy, although arterial hypertension developed during that time. Mental deterioration then began, and six months later she was readmitted in coma. A 23-day course of 20 mg. of A.C.T.H. daily was given (the method of administration is not recorded); her condition improved remarkably during the first ten days, but relapsed on the thirteenth day, and she died ten weeks later.

Blood transfusions have been given in 20 cases, with transitory or no benefit; Singer *et al.* (1950) pointed out that transfused cells appear to be as rapidly haemolysed as those of the patient. Christian's (1951) statement that transfusion of platelets has been reported as a successful treatment is erroneous; the case to which he referred (Hirsch *et al.*, 1950) was one of thrombopathic thrombocytopenia, a condition which is not related to thrombotic microangiopathy.

Penicillin has been tried in five cases and aureomycin in one case without any demonstrable effect. It is doubtful whether streptomycin was responsible for the remission which followed in the one case in which it was given (Symmers and Barrowcliff, 1951). Sulphonamides appear to have been seldom used; they have been either without effect or possibly detrimental (Engel *et al.*, 1947; Fitzgerald *et al.*, 1947).

Splenectomy was performed in six cases. The patients were already severely ill, and four died during or shortly after the operation; one survived for six days, and showed no improvement during this time. The sixth case was that of Meacham *et al.* (1951); the long remission following this splenectomy suggests that the operation deserves further trial at a stage before the patient's condition makes surgery unduly hazardous.

A.C.T.H. has been tried only in the case of Meacham *et al.* (1951); although this patient's second remission may not have been due to the treatment, trial of A.C.T.H. or cortisone in future cases is obviously indicated. The nature of the primary lesion of the vascular wall suggests a relationship between this disease and the so-called collagen diseases and encourages the hope for benefit from treatment with these hormones; it is similarly relevant that they are said to have caused remissions in some haemolytic anaemias (Selye, 1951). The dosage given by Meacham *et al.* (1951) was small; they suggested that larger doses might cause ischaemic complications. This objection is possibly fallacious; its basis was the observation of multiple small infarcts in cortisone-treated cases of polyarteritis nodosa, due supposedly to over-rapid healing of the vascular lesions. Infarcts are not in fact necessarily numerous in cases of polyarteritis so treated (Symmers and Litchfield, 1952); moreover, only the smallest vessels are affected in thrombotic microangiopathy, so that there is more opportunity for maintenance of adequate collateral circulation, and the vessels involved are by no means always completely occluded.

Anticoagulant therapy has not been used in any recorded case; its trial in patients with such a severe haemorrhagic tendency would require a difficult decision (Singer *et al.*, 1950).

Morbid Anatomy and Histopathology

Apart from evidence of severe anaemia and more or less widespread haemorrhages, which are usually petechial, there is little to be found macroscopically at necropsy. Some cases show small necrotic foci or infarcts in the viscera. The spleen may be moderately enlarged.

The microscopical findings are diagnostic. The characteristic histological feature is a very widely disseminated thrombosis of the smallest calibre blood vessels. Although the lesions may not be constantly present in any particular organ, they are particularly frequent and numerous in the myocardium, the capsular zone of the adrenals, and the renal cortex, and particularly rare in the lungs, where only the bronchial vasculature may be affected. The hepatic and adrenal sinusoids escape involvement.

The affected vessels are partly or completely occluded by granular or hyaline eosinophil material. Since the work of Baehr *et al.* (1936) it has usually been assumed that the occlusive masses are platelet thrombi (Editorial, 1950), although this remains unproved and the results of histochemical studies are equivocal (Orbison, 1952). The thrombus is often propagated free within the lumen for a considerable distance from its attachment to the vessel wall. It becomes covered by endothelium, and often a narrow crescent of lumen remains patent. Vessels which were completely occluded may be reopened by shrinkage of the thrombus away from the wall over part of its extent, or the thrombus may be canalized by endothelium-lined spaces. The older thrombi are more compact and may be invaded by endothelial cells or fibroblasts. The obstructed vessels may be much dilated and their walls very thin; Orbison (1952) showed that the dilatations are fusiform aneurysms involving the arteriolo-capillary junctional zone predominantly. Hyaline or sometimes fibrinoid material may be found beneath the endothelium of vessels of the size in which the thrombi form; this mural alteration has been described as the primary or prethrombotic lesion of the disease (Gore and Friedman, 1948; Gore, 1950), endothelial damage over the hyaline material leading to the deposition of platelets and so to the development of the characteristic thrombotic masses. There is doubt about the nature of hyaline projections into the lumen which may be seen in some cases; they may be focal protrusions from the hyaline prethrombotic lesion or they may possibly be old, shrunken, hyalinized thrombi. Further study of the mural changes is needed before this question can be decided. Endothelial hyperplasia is common even in vessels which are otherwise normal. Absence of any accumulation of inflammatory cells is characteristic; occasionally there is adjacent haemorrhage, but petechiae often seem to occur independently of demonstrable vascular lesions.

Small arteries, arterioles, and capillaries may be involved, although the arteriolo-capillary junctional zone is most often affected. Venules may contain the typical thrombi, although this is exceptional, and some authors claim that the supposed venules are dilated arterioles which have been misidentified. In the most heavily involved tissues the majority of the vessels may be affected, yet necrotic foci in the parenchyma are usually few and minute, and may be absent. Bernheim (1943) and others suggested that the relative paucity of ischaemic lesions could be explained by the incomplete occlusion of many affected vessels; collateral circulation through uninvolved vessels and recanalization of thrombi are other likely factors. In the kidneys the juxtaglomerular portion of the afferent arterioles is most often affected; glomerular capillaries are often obliterated by hyaline material which is not clearly thrombotic in nature but appears rather to represent a change in the capillary wall. A focal proliferative "glomerulitis" has been noted. The neurohistological changes have been described by Adams *et al.* (1948).

Differential Histological Diagnosis

The lesions of anaphylactoid purpura are easily distinguished from those of thrombotic microangiopathy by the cellular inflammatory reaction around the affected vessels in the former. Vascular lesions in some cases of "primary" amyloidosis may resemble the hyaline lesions of thrombotic microangiopathy fairly closely; their true nature is indicated by the changes elsewhere.

Lesions indistinguishable from the recanalized complete occlusions of thrombotic microangiopathy may be found in arterioles following occlusion of their parent arteries; such lesions are often seen in the vicinity of older arterial lesions of polyarteritis nodosa and occur particularly frequently in the subcutaneous tissue in arteriosclerotic gangrene and in acronecrosis associated with subacute bacterial endocarditis (Pagel, 1949), Raynaud's syndrome, and similar forms of peripheral ischaemia. The thrombi in these conditions are composed of erythrocytes and fibrin, unlike those of thrombotic microangiopathy, and it is interesting that they undergo identical morphological changes (hyalinization, retraction, surface endothelization, recanalization). Similar lesions, also probably originating as banal thrombosis, are seen in the vasculature of some gliosarcomata and occasionally in metastatic tumours in the brain; it is noteworthy that endothelial hyperplasia is a recognized characteristic of the vasculature of some of these tumours. Identical changes were shown in vessels occluded by agglutinated erythrocytes in experimental intoxication with certain snake venoms (Amorim *et al.*, 1951). Such observations suggest that the reparative process following thrombotic occlusion of these smallest-calibre vessels is similar, whatever the nature of the occlusive mass.

Aetiology

The cause of thrombotic microangiopathy is unknown. No infective agent has been found. Allergy has been suggested, without good evidence, although urticaria and joint pains have occurred prodromally and nasopharyngitis may precede the acute illness. Sensitivity to sulphonamides was suggested in one case (Fitzgerald *et al.*, 1947) and demonstrated in another, in which the evidence for its causal relation to the disease was equivocal (Engel *et al.*, 1947). The direct Coombs test was negative in the three cases in which it was performed, suggesting that haemolysis was not mediated through a globulin antibody. Reticulocytosis, leucocytosis, and the normality of megakaryocytes exclude "hypersplenism." No familial cases have been reported, although one patient's brother had idiopathic thrombocytopenic purpura without thrombotic lesions (Baehr *et al.*, 1936). Baehr *et al.* looked upon thrombotic microangiopathy as a variety of idiopathic thrombocytopenic purpura, but Klemperer (1951) has since accepted its primarily vascular nature.

Although it does not bring one much nearer to understanding the cause of the disease, the evidence for a relationship to the so-called collagen diseases is considerable, as Beigelman (1951) indicated. The morphology of the primary vascular lesion suggests such a relationship. One case of polyarteritis nodosa has been recorded in which widely disseminated lesions of thrombotic microangiopathy were also present, although there were no ante-mortem observations which could be related unequivocally to their presence (Symmers and Gillett, 1951). A family history of polyarteritis nodosa (Bernheim, 1943) and of disseminated lupus erythematosus (Singer *et al.*, 1950) has been reported. Relationship between disseminated lupus erythematosus and thrombotic microangiopathy has been much disputed, and was strongly denied by Klemperer (1948); while there are no close clinical or pathological similarities between them, "wire-loop" glomeruli have been noted in the latter, and three cases (Baehr *et al.*, 1936; Engel *et al.*, 1947; Meacham *et al.*, 1951) presented verrucose vegetations on the heart valves, resembling those of disseminated lupus erythematosus. One patient with thrombotic microangiopathy had had discoid lupus erythematosus of the scalp for ten years (Meacham *et al.*, 1951).

Jones and Loring (1951) suggested that thrombotic microangiopathy was merely an unusually severe form of capillary thrombosis such as occurs in the glomeruli and occasionally elsewhere in some cases of bacterial infection or circulatory disturbance, possibly through toxic or anoxic damage to the endothelium. Their argument is unconvincing.

Any aetiological theory must explain not only the primary vascular change which leads to thrombosis and thrombocytopenia but also the leucocytosis and haemolysis. Studies of many more cases during life are essential before the cause and nature of the disease can become clear.

Nomenclature

None of the names which have been used for this disease is satisfactory. Thrombocytic acroangiothrombosis (Fitzgerald *et al.*, 1947), thrombocytopenic thrombocytic microangiothrombosis (Lunedei, quoted by Vannucchi, 1949), generalized blood platelet thrombosis (Green and Rosenthal, 1949), and platelet thrombosis syndrome (Beigelman, 1951) assume the still unproved thrombocytic nature of the occlusive masses in the vessels. Moschcowitz's syndrome (Lennox and Dacie, 1951) shares with Beigelman's (1951) term the advantage of stressing the occurrence of a definite clinical picture, but has the objection of being eponymous. The most popular name, thrombotic thrombocytopenic purpura (Singer *et al.*, 1947), is inappropriate for those cases in which thrombocytopenia or purpura is absent. All these names neglect the characteristic haemolytic anaemia.

Thrombotic microangiopathic haemolytic anaemia, or, for brevity, thrombotic microangiopathy, is suggested as a suitable substitute for the names previously used. It indicates the location and the most striking feature of the characteristic histological lesions without mentioning inconstant and controversial features of this clinico-pathological entity.

Case 1

A previously healthy man aged 32, of independent means, had a febrile cold in February, 1946. He recovered in a few days, but a week later began to suffer from vague aching in the back and limbs. He felt off colour, was easily tired, and began to lose appetite. A few days later he noticed transient slurring of his speech on several occasions. One week later, on March 1, he was noticed to be fidgety, and confused about the identity of people whom he met. His doctor saw him next day and found him to be mildly disoriented; examination showed nystagmus and slight ataxia, a non-haemorrhagic urticarial rash, and a trace of protein in the urine. Two days later he seemed to be quite well, although it was noticed that a purpuric eruption appeared distal to the sphygmomanometer cuff. On March 10 he called on his doctor socially and fainted twice during the visit. He was admitted to hospital on the same evening.

On admission his temperature was 101° F. (38.3° C.) and pulse 140. He was pale and slightly jaundiced, and there were a few purpuric spots on his limbs. No other abnormality was found on systematic examination. His blood pressure was 135/75.

Investigations.—Erythrocytes 3,200,000 per c.mm.; reticulocytes, 22%; haemoglobin, 9.3 g. per 100 ml.; leucocytes, 12,800 per c.mm., with 75% (9,600) neutrophils, 2% (256) eosinophils, 18% (2,304) lymphocytes, and 5% (640) monocytes; 12 normoblasts were noted in counting 300 leucocytes; platelets, 84,000. The serum bilirubin was 6.5 mg. per 100 ml.; plasma proteins, 6.2 g. (albumin 3.2 g., globulin 3 g.); blood urea 34 mg. per 100 ml. Urine: protein ++; urobilinogen ++; no bilirubin or reducing substance; many erythrocytes and occasional granular casts in centrifugate.

On March 11 his temperature was 102° F. (38.9° C.) and pulse 140. He complained of stiffness of the left hand. The left biceps and triceps reflexes were exaggerated; the tendon reflexes of the right arm and of both legs were normal, although there was an extensor plantar reflex on the right side. During the day purpura became widespread and there was frank haematuria. Successive platelet counts at intervals of a few hours were 210,000, 34,000, and 78,000. On March 12 he was stuporous; the reflexes were now normal, but a partial left facial paralysis was noted and the right pupil was contracted and immobile. His condition

deteriorated rapidly; his temperature rose to 107° F. (41.7° C.) shortly before death and both pupils became widely dilated. Investigations within a few hours of death showed 4.1 g. haemoglobin, 1,400,000 erythrocytes, with 36% reticulocytes, 4,000 platelets, and 23,000 leucocytes. No myelocytes, premyelocytes, or myeloblasts were seen; 49 normoblasts were counted per 300 leucocytes. The blood urea was 36 mg. per 100 ml.

Necropsy.—The noteworthy macroscopical findings were anaemia, jaundice, and widespread purpura in the skin, serosae, and urinary and intestinal tracts; permission to examine the brain was withheld. *Microscopical findings:* The histological appearances were typical of thrombotic microangiopathy (Fig. 1). Lesions were particularly numerous in the outer third of the ventricular myocardium, and in the adrenals, renal cortex, and pancreas. There were a few minute foci of necrosis in the myocardium, without any cellular infiltration.

Comment.—The clinical picture illustrated the characteristic features of this disease, and the diagnosis could have been made during life. The illness probably dated from the "cold," a month before death, although the patient seemed to be in good health when he fainted, 46 hours before he died. While it is now recognized that the histological findings were typical of thrombotic microangiopathy, it should be admitted that two years passed before they were identified. Many pathologists saw the sections and, while all appreciated the seemingly unique nature of the vascular changes, none was acquainted with the disease. Only later, when illustrations of identical lesions were found in a paper about this condition, was the diagnosis made.

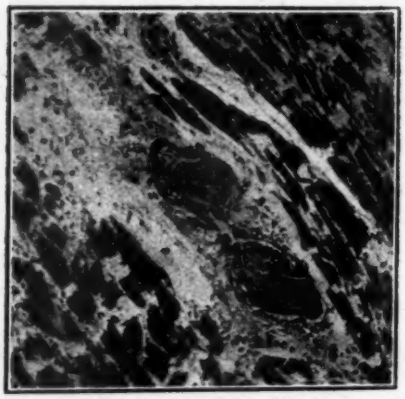

Fig. 1.—Case 1. Irregular dilatation and partial or complete thrombotic occlusion of arterioles and capillaries in myocardium. Endothelization and partial organization of some of the granular or hyaline thrombi. (Haematoxylin and eosin. ×100.)

Case 2

A wood machinist aged 27 had an inguinal herniorrhaphy on July 31, 1951; previously his health had been excellent, and he seemed to be perfectly well when he was discharged home on August 9. On August 18, while he was sitting quietly at home, he suddenly threw up his arms and said, "Send for a doctor." He made no complaint, but repeated his demand several times before collapsing on to the floor, where he vomited and then lay still. His doctor found him deeply unconscious; his limbs were flaccid, although the plantar responses were extensor. Within a few minutes the coma became less deep and he responded to some commands. He was admitted to hospital a few hours later.

On admission he was semiconscious. He resisted examination, answered some questions and ignored others, and on one occasion let himself fall to the floor with seemingly deliberate care to avoid hurt. His general behaviour suggested hysteria, but it was observed that there was paralysis of movement of the left eye to the right, a pin-point left pupil, and no pupillary reaction to light on either side. All reflexes were brisk; the plantar responses were now flexor and muscle tone was normal. Examination of the other systems showed no abnormalities except for regular coupling of the pulse beats; the pulse rate was 64, the blood pressure 110/70.

Investigations.—Urine: trace of protein; no sugar. Lumbar puncture: clear colourless cerebrospinal fluid under normal pressure; 70 mg. of protein per 100 ml.; Lange curve 0012100000; no cells found.

When re-examined an hour after admission both pupils were moderately dilated and reacted to light. There was now spontaneous nystagmus to the left and no evidence of ocular palsy. He was stuporous until his death on August 20, 54 hours after he collapsed at home. While in hospital he was noticed to become increasingly pale; the blood was not examined. There was no jaundice or pyrexia. His pulse rate ranged between 50 and 80; coupled beats were not found after the first few hours of observation. An electrocardiogram on the day of his death showed sinus rhythm, rate 50, with occasional ventricular extrasystoles and left axis deviation.

Necropsy.—There were four small petechiae in the skin and scattered petechiae in the serosae. The meninges, dural sinuses, and cerebral arteries were normal. A single fresh haemorrhage 0.3 cm. in diameter, was found in the left caudate nucleus; the brain was slightly oedematous but otherwise normal, and there was no trace of a pressure cone. No venous thrombosis, pulmonary embolism, or other noteworthy abnormalities were found, and the interatrial foramen was closed. The bladder urine gave strong reactions for urobilinogen and urobilin. *Microscopical findings* (Fig. 2): Typical vascular lesions of thrombotic microangiopathy were present in the brain, particularly in the subcortical zone and in the medulla, and also in the myocardium, portal tracts, and kidneys. In addition, many small arterioles which were not thrombosed showed segmental hyaline change or endothelial hyperplasia. Many glomeruli showed patchy hyaline obliteration of some loops, and there was some periglomerular fibrosis. No necrotic foci were found in any of the organs.

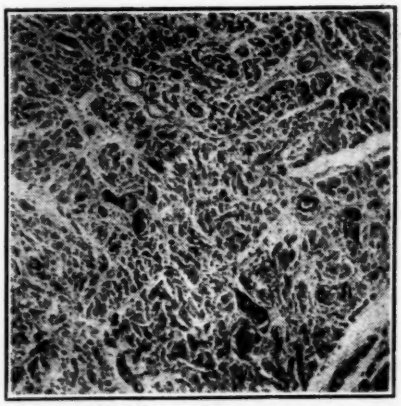

Fig. 2.—Case 2. Thrombosis of many smallest-calibre vessels in myocardium. (Haematoxylin and eosin. ×80.)

Comment.—This case was clinically atypical. There were no prodromata, and the total duration of illness was 54 hours. The presenting manifestations simulated hysteria, but abnormal neurological signs were present. While the latter were transient and to some extent fluctuating in localization, these qualities were not so pronounced as to be diagnostic. No haemorrhagic tendency was noted during life, and petechiae were not a striking feature at necropsy. While anaemia developed during the period of observation, it was not serious enough clinically to give rise to concern, and no evidence of haemolysis was noted before death, although the urine obtained *post mortem* contained excess urobilinogen.

Summary

Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy) is the name proposed for an unusual disease, possibly related to the so-called collagen diseases, and commonly referred to as thrombotic thrombocytopenic purpura. The fully developed clinical syndrome consists of fever, haemorrhagic manifestations, haemolytic anaemia, and multifarious *fluctuating* signs of neurological disorder. This tetrad

is diagnostic, but often is complete only in the terminal stages of the illness, and any component may be absent. The disease should be considered in the diagnosis of all cases which present the association of haemolytic anaemia and thrombocytopenic purpura; biopsy may be of value.

Examination of the tissues shows a unique histological picture of widely disseminated thrombosis of the smallest-calibre blood vessels, with endothelial hyperplasia, conspicuous dilatation of many of the affected vessels, and no inflammatory reaction.

The disease has been fatal in every case which has been reported. Treatment with A.C.T.H. or cortisone deserves trial, and splenectomy should be considered.

Two new cases are reported.

I wish to thank the many colleagues who have been patient with my interest in this disease, particularly Dr. D. F. Barrowcliff for his help in reviewing the literature, and Dr. D. R. Humphreys for allowing me to report the case of his patient (Case 2).

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NEWER SYNTHETIC ANALGESIC DRUGS

BY

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During the last ten years a group of new synthetic analgesic drugs has become available to the medical profession. The purpose of this paper is to present the results of a comparison made between the individual members of this group of new drugs, and between them and morphine. The drugs of the new series are:

Pethidine ("dolantin," "dolantal," "demerol," "meperidine") 1-methyl-4-phenylpiperidine-4-carboxylic-acid ethyl ester hydrochloride.

Amidone ("physeptone," "miadone," "dolophine," "methadon") DL-6-dimethylamino-4:4-diphenylheptan-3-one hydrochloride.

Phenadoxone ("heptalgin," "heptazone") DL-6-morpholino-4-:4-diphenylheptan-3-one hydrochloride.

Höchst 10581 (for purposes of convenience it will be referred to here as "hexanone") DL-6-morpholino-4:4-dipheny-hexan-3-one hydrochloride.

Patients suffering from the following painful conditions were used: post-herpetic neuralgia, tuberculous cystitis, pubic osteitis, sciatic pain due to prolapsed intervertebral disk, rheumatoid arthritis, ankylosing spondylitis, lymphosarcoma with abdominal pain, and carcinoma of the cervix, vagina, colon, stomach, glossotonsillar sulcus, larynx, breast, and bronchus, with metastases in the spine. The effect of these analgesics was not investigated on the following pains for the reasons given: the pains associated with coronary thrombosis, trigeminal neuralgia, burns, or childbirth, as the pain is insufficiently chronic; the pains associated with colic or peptic ulcer, as they are best treated with spasmolytic drugs; the pain of headache, as many different types of pain might be included under this heading, including psychogenic pain. The conclusions drawn in this work, then, do not refer to these pains. In most patients tested the pains were severe; only in those with rheumatoid arthritis and ankylosing spondylitis was this not so. In all patients the pain was chronic, and never disappeared spontaneously. Unless some analgesic drugs were given, sleep or occupations such as reading were impossible in all patients, except those with rheumatoid arthritis or spondylitis.

Morphine, being a well-known and effective analgesic, was compared with the newer group of drugs. It was given by injection intramuscularly, in the form of the sulphate or as papaveretum ("omnopon"), or by mouth as the hydrochloride, as "nepenthe," or as papaveretum. The new drugs were given orally in tablet form or intramuscularly.

The method of clinical assessment was that reported by Keele (1948), by Hewer, Keele, Keele, and Nathan (1949), and by Robson and Keele (1950). Trials were carried out on a few patients whose pains were constant over periods of weeks and who were able to keep pain charts. These patients were given various drugs and inert substances, and recorded hourly the state of their pain, using the categories severe, moderate, slight, or nil. The method is entirely subjective. The results obtained on

each patient with certain doses and drugs were compared with those obtained by using other doses and drugs. A minimum of 10 administrations of each dosage of a drug given to one patient had to be attained before the results were incorporated in the series; in many patients 40 to 50 administrations were made. It is believed that valuable information on the effectiveness, speed of onset, and duration of effect of analgesics is obtainable from many administrations of various substances to such reliable witnesses. As the patients did not know what drug or what dosage they were receiving on any occasion, each administration of an analgesic drug formed a valid experiment comparable with every other administration to the same patient. As many as four experiments could be carried out on one patient in a day; and so, although the number of patients used was only 75, the number of results on each satisfactory witness was large enough for statistical analysis. A possible source of error in the method is due to spontaneous variations in the intensity of pain during the course of a series of administrations. With every patient pain charts have been kept occasionally while no drugs were given, so that such spontaneous fluctuations in the categories of pain might be observed. As mentioned, all patients were given inert substances in order to exclude a possible psychological factor responsible for the relief of pain.

Equiactive Doses

Once a substance has been shown to have analgesic properties it is necessary to determine the dose which gives an effect similar to the usual dosage of well-established analgesics. In assessing the value of analgesics such factors as toxicity, absorption, and effects on certain kinds of pain and not on others have been taken into consideration. The actual equiactive doses found by trial and error of the various drugs are presented first; then possible and useful doses, taking into account toxicity and side-effects; and, finally, maximum tolerated doses and minimal effective doses.

Equiactive doses were calculated for each patient from the various doses given. To most patients the drugs being tested were given in some such scheme as the following: drug A was given for two days, drug B for three days, drug A again for two days, and then drug B for one day. In some instances drug A would be given for a certain time and be followed by drug B; but in other instances drug B would be the first and be followed by drug A. If a given dose of a drug failed to bring any relief it was not included for comparison with other drugs, for comparisons could be made only with doses that were effective.

Figures for statistical analysis were obtained by using the following criteria of failure and success. For each dosage of each drug the number of times the pain was reduced from severe to nil, and/or the number of hours the pain remained at or returned to severe within six hours of administration, and/or the number of hours the pain remained slight or nil, within six hours of administration, were extracted from the charts. Such figures were compared with those obtained when giving another drug to the same patient. By the use of these criteria, from each dose of each drug a certain number of successes and of failures were obtained; and from these a 2 by 2 contingency table was made for each dosage. The tests of significance used were that described by Pearson (1947) and Yates's modification of the χ^2 test ($P>0.05$). For example, in one patient 100 mg. of pethidine reduced the pain from severe to nil 8 times out of 10, and 60 mg. of phenadoxone reduced it from severe to nil in 8 out of 14 times; these doses were taken to be equiactive. In this same patient 10 mg. of amidone reduced the pain in 34 out of 34 trials; this difference in the number of times the pain was reduced from severe to nil by 10 mg. of amidone and 60 mg. of phenadoxone was greater than might be expected were these doses equiactive; and so 10 mg. of amidone was taken to be more effective than 60 mg. of phenadoxone.

All the drugs tested, if given by injection, caused a definite analgesic effect within half an hour; when given orally the results were less consistent. These differences were indicative not of the efficacy of the drug but rather of the variability of the patient. In only a few patients did any drug fail to have some analgesic effect within the half-hour; the rapidity with which analgesia is achieved is related more nearly to the degree and type of pain and to the personality of the patient than to the drug or its dosage.

For the sake of brevity, the charts, the figures culled from the charts, and most of the tables of equiactive doses are not shown. Three of the tables are given as examples. Table I shows the equiactive doses of amidone and morphine, as judged by the reduction of pain from severe to nil. Table II shows the equiactive doses of amidone and pethidine, as judged by the number of hours the pain remained severe within six hours of administration. Table III shows the equiactive doses of phenadoxone and pethidine, as judged by the number of hours the pain was slight or nil within six hours of administration. Only the actual equiactive dosages are shown; the many figures scattered on each side of the equiactive amounts are not given, and they have not been used in the calculations. From these tables the following equiactive dosages were found.

Comparing amidone and morphine, the mean of the dosages employed was 18 mg. of amidone equiactive with 23 mg. of morphine. The limits of scatter were 15 mg. of amidone equiactive with 16 mg. of morphine, and 30 mg. of amidone equiactive with 64 mg. of morphine. Thus for

Table I.—*Equiactive Doses of Amidone and Morphine, as Judged by Reduction of Pain from Severe to Nil*

Patient	Dosages having Equal Analgesic Effect Amidone : Morphine or derivative
Col	20 mg. (parenteral) = ⅓ gr. (32 mg.) (parenteral)
Pa	20 mg. (parenteral) = ⅓ gr. (32 mg.) (parenteral)
Ha	20 mg. (parenteral) = ⅓ gr. (32 mg.) (parenteral)
Ma	20 mg. (parenteral) = 30 min. (1·8 ml.) nepenthe (oral)
Ml	20 mg. (parenteral) = 30 min. (1·8 ml.) nepenthe (oral)
Be	20 mg. (parenteral) = 30 min. (1·8 ml.) nepenthe (oral)
Ph	10 mg. (oral) = 15 min. (0.9 ml.) nepenthe (oral)
Hu	10 mg. (oral) = 25 min. (1.5 ml.) nepenthe (oral)
Mu	10 mg. (oral) = ¼ gr. (16 mg.) (parenteral)
Ca	10 mg. (parenteral) = 2/3 gr. (45 mg.) papaveretum (parenteral)
W	20 mg. (oral) = 2/3 gr. (45 mg.) papaveretum (oral)
Ba	15 mg. (oral) = ¼ gr. (16 mg.) (parenteral)
L	15 mg. (parenteral) = ¼ gr. (16 mg.) (parenteral)
Pe	30 mg. (parenteral) = ¾ gr. (48 mg.) (parenteral)
R	30 mg. (parenteral) = 1 gr. (65 mg.) (parenteral)

Table II.—*Equiactive Doses of Amidone and Pethidine, as Judged by Number of Hours Pain was Severe within Six Hours of Administration*

Patient	Dosages Having Equal Analgesic Effect Amidone : Pethidine
T	10 mg. (oral) = 100 mg. (oral)
K	10 mg. (oral) = 150 mg. (oral)
Coo	10 mg. (parenteral) = 200 mg. (oral)
Ca	10 mg. (oral) = 150 mg. (oral)
Hu	20 mg. (parenteral) = 100 mg. (oral)

Table III.—*Equiactive Doses of Phenadoxone and Pethidine, as Judged by Number of Hours Pain was Slight or Nil within Six Hours of Administration*

Patient	Dosages Having Equal Analgesic Effect Phenadoxone : Pethidine (all oral)
L	30 mg. = 100 mg.
Ch	40 mg. = 50 mg.
Cu	40 mg. = 50 mg.
E	45 mg. = 100 mg.
H	50 mg. = 100 mg.
Co	55 mg. = 100 mg.
P	60 mg. = 100 mg.

practical purposes 18 mg. of amidone may be taken as analgesically equivalent to ¾ gr. (24 mg.) of morphine; 12 mg. of amidone is roughly equivalent to ¼ gr. (16 mg.) of morphine, and 25 mg. of amidone to ½ gr. (32 mg.) of morphine.

Comparing pethidine and morphine, the mean of the dosages employed was 125 mg. of pethidine equiactive with 16 mg. of morphine. The limits of scatter were 100 mg. of pethidine equiactive with 32 mg. of morphine, and 200 mg. of pethidine equiactive with 16 mg. of morphine. Thus for practical purposes 125 mg. of pethidine can be regarded as equivalent to 16 mg. of morphine.

Comparing phenadoxone and morphine, the mean of the dosages employed was, when the drugs were given by injection, 10 mg. of phenadoxone equiactive with 16 mg. of morphine, and when the drugs were given by mouth, 55.5 mg. of phenadoxone equiactive with 16.6 mg. of morphine. The limits of scatter for the oral dosages were 60 mg. of phenadoxone equiactive with 22 mg. of morphine, and 50 mg. equiactive with 10 mg. of morphine. Thus when the drugs are given by injection 10 mg. of phenadoxone is equivalent analgesically to 16 mg. of morphine; but when they are given orally, roughly 50 mg. of phenadoxone is equivalent to 16 mg. of morphine.

Comparing amidone and pethidine, the mean of the dosages employed was 12 mg. of amidone equiactive with 130 mg. of pethidine. The limits of scatter were 10 mg. of amidone equiactive with 200 mg. of pethidine and 5 mg. of amidone with 100 mg. of pethidine, and at the other extreme 20 mg. of amidone equiactive with 100 mg. of pethidine and 15 mg. of amidone with 75 mg. of pethidine. Thus for practical purposes 10 mg. of amidone may be regarded as equivalent to 100 mg. of pethidine.

Comparing phenadoxone and amidone, the mean of the dosages employed was, when the drugs were given by injection, 10 mg. of phenadoxone equiactive with 10 mg. of amidone, and, when the drugs were given by mouth, 50 mg. of phenadoxone equiactive with 7.8 mg. of amidone. The limits of scatter for the oral dosages were 50 mg. of phenadoxone equiactive with 5 mg. of amidone and 50 mg. equiactive with 10 mg. of amidone. Thus for practical purposes 50 mg. of phenadoxone may be taken as equivalent to 7.5 mg. of amidone.

Comparing phenadoxone and pethidine, the mean of the dosages employed was 47 mg. of phenadoxone equiactive with 84 mg. of pethidine. The limits of scatter were 40 mg. of phenadoxone equiactive with 50 mg. of pethidine and 30 mg. of phenadoxone with 100 mg. of pethidine. Thus for practical purposes about 25 mg. of phenadoxone may be regarded as equivalent to 50 mg. of pethidine.

Comparing phenadoxone and hexanone, the mean of the dosages employed was 42 mg. of phenadoxone equiactive with 40 mg. of hexanone; and the scatter was only 45 mg. of phenadoxone equiactive with 30 mg. of hexanone. For practical purposes these two drugs may be regarded as analgesically equal.

The results obtained when using phenadoxone and hexanone by mouth have been less consistent than those obtained with the other drugs. The probable effect of these drugs given orally could never be foretold: a dose of 60 mg. of either of them could be adequate in one patient and almost useless in the next one. This kind of inconsistency has not been found with any of the other drugs; though they might be found useless on account of unpleasant side-effects, the analgesic effect could be foretold. This discrepancy is not shown in the tables. For often a dose such as 40 mg. would be found no better than an inert substance; when this occurred the number of experiments would necessarily be so few that no useful conclusions could be drawn. The great variability in the effectiveness and toxicity of these two drugs is probably due to variability in absorption. Such inconsistencies, however, do not mean that these two drugs are always useless. In some patients, when the dose has been adequate, they have been found to be useful and satisfactory analgesics.

Duration of Analgesic Effect

In order to examine the duration of the analgesic effect of the various dosages of the different drugs more closely, 15 of the most satisfactory witnesses were used. For each patient the drugs were placed in the order of efficiency. The criterion employed was the total number of hours the pain remained in a lower category than that at which it was when the drug was given, six hours being regarded as the maximum possible time. At least six trials were made for each dosage used; usually at least 12 trials were made.

From these results the following facts were obtained: hexanone has a longer-lasting analgesic effect than phenadoxone in the same dosage, and phenadoxone is a poor analgesic from this point of view. Amidone always has a longer-lasting effective action when given parenterally than when given orally.

Toxicity and Side-effects

As only a few patients have been used in this investigation, information about toxicity and side-effects needs to be seen as only suggestive.

The toxic effects of the four new drugs investigated were largely confined to symptoms. Repeated blood counts were carried out on patients who had these drugs for periods of up to a year; no toxic effects were found on the red or white cells or the platelets. In the doses used no form of skin eruption, no allergic manifestations, and no depression of respiration were encountered.

Symptoms severe enough to cause the administration of the drugs to be stopped were sleepiness, lassitude, a dull mental state that the patients usually described as "the pills make me feel dopy," nausea and vomiting, severe anorexia, dizziness, a sensation of "swimminess in the head," vertigo, tinnitus, headache, sweating, dryness of the mouth. All these symptoms were obtained in a marked degree when the drugs were given intravenously, showing that the prominent side-effects of nausea, vomiting, and anorexia were not due to an irritant effect on the alimentary canal. Objectively, the only sign that occurred more than once consisted in myoclonic jerks.

Three patients had transient disturbances of cerebration. One of them had been on amidone four-hourly for a fortnight without any toxic effects; one evening she got a temperature of 103.5° F. (39.7° C.), due to an infection, and had two attacks of vertigo, associated with a feeling of psychological remoteness and some confusion; at the same time the usual noises of the ward appeared to her to be insupportably loud. However, amidone was given regularly after this episode, the temperature never again reaching this height, and she never again had a similar attack. It cannot be known whether this episode was due to the fever alone or to the combined effects of fever and amidone. Another patient after receiving 20 mg. of phenadoxone by injection became confused; with 10 mg. by injection she said that all her thoughts became jumbled up and she felt dazed; it was noted that no similar effect was obtained when she took 70 mg. by mouth. Another patient after having more than one dose of 20 mg. of amidone by injection in 24 hours always had slight confusion, hallucinations, and delusions: she imagined that she was holding a cup of tea, when nothing was in her hand, and believed that she was about to be discharged from hospital, whereas in fact she had not yet had the operation for which she had been admitted.

The side-effects due to the new analgesic drugs are largely the same as those due to morphine and its derivatives. The exception is myoclonic jerks, which have not been seen to follow the administration of morphine. In large doses morphine may cause difficulty in starting micturition; this has not been seen after the administration of the newer drugs. Euphoria has only very rarely been seen in these patients having chronic pain; but it has occurred with

morphine, amidone, and phenadoxone. Although, in general, the presence of toxic symptoms is related to dosage, 10 out of 33 patients who received pethidine, amidone, and phenadoxone had the toxic symptoms mentioned above with all these drugs, and at dosages inadequate to give analgesia.

Approximately one-third of all patients having morphine or its derivatives had the same symptoms. Some were unable to take any of the synthetic drugs tested or morphine and its derivatives owing to the side-effects. With all the drugs investigated light-headedness, nausea, and vomiting were found to be more likely to occur if the patient was up than if he was in bed, and if he sat up and moved about than if he lay still.

It was found that no single one of the new drugs investigated was constantly more toxic than any other. Each of the four drugs caused toxic symptoms in some patients, although the other three could be taken.

The question of toxicity is obviously intimately bound up with dosage. On the whole, a patient who can take one member of the new synthetic group of drugs is likely to be able to take small doses of any other member of the group. Nevertheless, one patient was seen who could take 50 mg. of pethidine yet could not take 40 mg. of phenadoxone; she could not keep awake and suffered from nausea with as small a dose as 2.5 mg. of amidone. Many patients could take 50 mg. of pethidine orally but could not take 50 mg. by injection. All those patients who could take amidone were able to take 10 mg., whereas higher doses might not be tolerated. With regard to phenadoxone, all those who could not tolerate 10 mg. by injection could take 70 mg. by mouth; in fact, in this investigation the maximal oral dose of phenadoxone or hexanone has not been discovered, for 70 mg. of either drug taken orally was tolerated by some subjects. The maximal doses used are given in Table IV.

TABLE IV

Name of Drug	Maximal Tolerated Dosages	
	Maximal Single Doses	Maximal Dosage in 24 hours
Hexanone	70 mg. oral 20 mg. parenteral	360 mg. oral
Phenadoxone	70 mg. oral 20 mg. parenteral	420 mg. oral
Amidone	30 mg. oral 30 mg. parenteral	180 mg. oral 180 mg. parenteral
Pethidine	250 mg. oral 200 mg. parenteral	1,250 mg. oral 1,000 mg. parenteral
Morphine	192 mg. (3 gr.) parenteral	384 mg. (6 gr.) parenteral
Nepenthe	30 min. (1·8 ml.) oral	150 min. (9 ml.) oral
Heroin	8 mg. (⅛ gr.) parenteral	40 mg. (⅝ gr.) parenteral
Papaveretum	43 mg. (2/3 gr.) oral and parenteral	215 (3⅓ gr.) oral and parenteral

As toxic effects are symptoms rather than signs, attention was paid to the comments of patients having the various drugs. Sometimes no difference was noted between two drugs, particularly within the group of synthetic drugs. As patients were not told when another drug was being given, such comments were not sought, but they were noted when they were made spontaneously. Certain preferences were shown: 12 patients preferred amidone to morphine and 2 preferred morphine to amidone; 6 preferred amidone to pethidine and 3 preferred pethidine; 5 preferred pethidine to phenadoxone and 2 preferred phenadoxone.

It is useful to have analgesics that dull mental activity and tend to bring on sleep, and others that do not do so. All the new drugs investigated and the morphine group of drugs, when given in doses adequate to cause analgesia, have some tendency to cause drowsiness. If drowsiness is taken to be different from a tendency to sleep and to be a state of some clouding of general perception and alertness—a state that some patients liked and others disliked—it is found that of the 32 patients who had all the new drugs and morphine and nepenthe, 10 became drowsy; 2 were drowsy on all the drugs, 5 were drowsy on morphine but not on the new drugs, and 3 were drowsy on the new drugs but not on morphine or nepenthe. No evidence was found to support the common belief that amidone interferes less with a patient's alertness than morphine. One cannot foretell how a given patient will react to these drugs: one patient will fall asleep on one group of drugs, whereas another will be awake and free from pain on the same drugs but will fall asleep on the other group. Further, some will tend to fall asleep on 2.5 mg. of amidone, while others will not sleep on 30 mg.; some will be drowsy on 100 mg. of pethidine, others will be vigilant on 250 mg. four-hourly. Neither drowsiness nor falling asleep in the daytime has been caused by the oral doses employed of phenadoxone or hexanone. It is likely that insufficient dosage of these drugs was used, the reason being that the dosage was based on the results of injecting them into rats. As these drugs are so much less reliable when given orally to humans, the results of rat experiments were not transferable to man.

It will be seen that the problem of providing analgesic drugs that will always cause dulling of alertness and sleepiness, and drugs that will never do so, has not been solved.

There is a tendency for all the new drugs and morphine and related drugs to cause constipation, but this has rarely been a complaint of consequence. The spasmolytic action of these new synthetic drugs has not been investigated.

It will be understood from this section on side-effects that the search for the perfect analgesic drug has certainly not reached its end. All of the drugs investigated have been found to be useful in some patients. And also, if it is found that a certain patient cannot take any one drug he may be able to take all, none, or any one of the others tested here.

Useful Effective Doses

In practice equiactive doses, judged by criteria previously described, are not equally efficacious, because of the side-effects that are common to all these analgesic drugs. For example, 200 mg. of pethidine may not in fact give an analgesic effect similar to 20 mg. of amidone, for it may cause such vomiting and dizziness that the patient refuses to take it. One patient in this series, who needed 32 mg. of morphine for the relief of her pain, preferred to stand the pain without any analgesic drug rather than have the unpleasant effects accompanying 20 mg. of amidone or phenadoxone intramuscularly. Thus side-effects fix a ceiling to dosage; the heights of different ceilings permit larger amounts of one drug to be taken than equivalent amounts of another.

Although the analgesic effect of a dose of pethidine is the same whether given orally or intramuscularly, yet the same dose may be tolerated orally but not intramuscularly. Presumably, when the drug is given parenterally it reaches a higher level in the blood stream than when given orally. Although 30 mg. of phenadoxone intramuscularly gives the same analgesic effect as 30 mg. of amidone intramuscularly, this dose of amidone has often been given without undue depression of respiration, but this dose of phenadoxone is lethal. Hewer (personal communication) gave 30 mg. intramuscularly to a man of 70; in three minutes respiration stopped completely, and the pulse became weak in spite of efficient artificial respiration; nikethamide, 10 mg., had a transitory stimulating effect lasting three to four minutes, after which the patient's condition relapsed; in spite of three further injections of 10 mg. of nikethamide, spontaneous respiration did not return for 45 minutes.

The practising doctor is not concerned with the log-dose-response graphs of two or more analgesics; he wants to know equivalent doses of the drugs within the range of the usual practical dosages.

In considering useful effective doses, we may reckon that the traditional ¼ gr. (16 mg.) of morphine has the same analgesic effect as 12 mg. of amidone or 125 mg. of pethidine, whether the drugs are given by mouth or by injection; it is equiactive with 10 mg. of phenadoxone or

hexanone when these drugs are given by injection. Of nepenthe, 25 min. (1.5 ml.) may be reckoned to be equivalent to ¼ gr. (16 mg.) of morphine. As phenadoxone and hexanone are so unreliable when given orally it is meaningless to give equiactive doses for any route other than parenteral.

The suggested upper and lower limits of useful single doses of these drugs are given below, the upper limit being fixed in nearly all cases by intolerable side-effects and the lower limit by analgesic ineffectiveness.

Morphine	¼ to 1 gr. (11 to 65 mg.), oral or parenteral
Nepenthe	10 to 30 min. (0.6 to 1.8 ml.)
Amidone	5 to 30 mg., oral or parenteral (with slight pain, 2.5 mg. is sometimes enough)
Pethidine	50 to 250 mg. oral or parenteral
Phenadoxone	30 to more than 70 mg. oral; no upper limit has yet been found. 10 mg. parenteral. By injection, 20 mg. may be dangerous
Hexanone	As for phenadoxone

Addiction

Circumstances were favourable in this investigation for going into the question of addiction to morphine and amidone. All patients receiving large doses of these drugs over a long period had cancer; they were therefore a sample of the population unselected from a psychological standpoint and no more psychopathic than any average sample. Further, these patients were all in hospital for pain-relieving operations. After the operation no more of the drug to which they were accustomed was given. Before one can consider addiction in a patient having pain it is necessary to stop the pain, for any patient will ask for a drug that experience has taught will relieve the pain. Some patients would, under the stress of pain, impotence, and frustration, break down and cry when the drug that they usually had was withheld; it might have been concluded that they were addicted to the drug in question. But the opportunity of seeing these patients after a successful pain-relieving operation has shown that this was not so. These patients have not asked for a single dose of the drug once the pain had gone. They were neither addicted psychologically nor had they acquired physical dependence. (It is possible that the withdrawal syndrome made its appearance during the first 40 hours after the operation, while the patients were miserable and unwell anyway; but certainly no tremor was seen or any psychological distress.) In one patient the operation failed. He had been having amidone orally for months before the operation, and continued to ask for it after the operation.

These facts are not to be taken to indicate that addiction depends on only psychological factors, for it is known that once addiction has become established metabolism is carried on efficiently only in the presence of the drug or some similar drug. Nevertheless, experience with 12 patients in whom pain-relieving operations were successful has shown that none of them asked for or received any more analgesic drug after operation, although they had been receiving large doses before.

The amounts received by these patients are as follows:

Mrs. C ..	Amidone, 5,400 mg. in four to five months; phenadoxone, up to 300 mg. a day—about 9,000 mg. in same five months
Mr. Ph ..	Amidone, 5,000 mg. in 120 days
Mr. Sa ..	Amidone, 4,500 mg in 100 days
Mrs. Sy ..	Amidone, 4,305 mg. in 82 days
Mrs. R ..	Amidone, 3,600 mg. in 60 days; morphine 30 gr. (2 g.) in 30 days
Mr. J ..	Amidone, 1,200 mg. in 42 days
Mrs. Sm. ..	Over a period of years, but not every day: amidone, 50 mg. a day; phenadoxone, 250 mg. a day; and pethidine, 500 mg. a day
Mr. Pe ..	Amidone, 600 mg. in 90 days
Mrs. Ma ..	Amidone, 430 mg. in 22 days
Mrs. A ..	Amidone, 410 mg. in 30 days
Mrs. F ..	Morphine, 60 gr. (4 g.) in 120 days
Mrs. C ..	Morphine 30 gr. (2 g.) in 60 days.

This section is not meant to imply that these drugs are not drugs causing addiction. It is well known that they are. But most patients with severe pain can take large amounts of them without becoming addicted, provided their pain is relieved in some other way.

Comparison Between these Results and Reports from Other Investigations: Equiactive Doses

Batterman and Himmelsbach (1943), using the Woolf–Hardy apparatus, found that 75 mg. of pethidine given intramuscularly was ar effective analgesically as 10 mg. of morphine; this is the same equivalence as I found. In clinical trials, however, Batterman (1943) found that 100 mg. of pethidine had the same analgesic potency as 10 mg. of morphine. Batterman and Himmelsbach claimed that pethidine is superior to morphine because it is destroyed so rapidly that it is not cumulative, because it is less likely to cause addiction, and because it has a spasmolytic effect, whereas morphine may cause spasm. Van Dyke (1949) reported that 100 mg. of pethidine given parenterally approached the analgesic potency of 10 mg. of morphine. With regard to amidone, he thought that compared with morphine it caused "less sedation, less respiratory depression, and euphoria less frequently. It appears not to cause constipation." He concluded that amidone "is the most desirable analgesic for the treatment of pain in the chronically ill provided that a drug as powerful as morphine is required."

Scott, Kohlstaedt, and Chen (1947) found that in man 5 mg. of amidone had the same analgesic potency as 100 mg. of pethidine and 40 mg. of hexanone; I found that 5 mg. of amidone was equiactive with 50 mg. of pethidine. They also stated that amidone was approximately twice as potent as morphine, whereas I found it to be 1½ times as potent. Bercel (1948) stated that 15 mg. of amidone seemed to have the same analgesic effect as 15 mg. of morphine sulphate or 100 mg. of pethidine. In the present investigation 15 mg. of amidone was found to be equiactive with 20 mg. of morphine or 150 mg. of pethidine. Troxil (1948) discovered that 10 mg. of amidone was more effective than 150 mg. of pethidine and that 10 mg. of amidone was equiactive with 15 mg. of morphine, whereas I found it to be slightly less effective than 15 mg.

Wilson and Hunter (1948) reported that 20 mg. of phenadoxone was a fairly satisfactory analgesic when taken orally. In the present investigation doses of 30 mg. or less were found to be useless.

Summary

In clinical trials on patients with chronic pain, a comparison has been made between the following drugs: morphine and its derivatives, pethidine, amidone, phenadoxone, and Höchst 10581.

The doses of these drugs found in practice to have equivalent analgesic action are given.

Morphine and its derivatives, pethidine, and amidone can be relied on to give effective analgesia; phenadoxone and Höchst 10581 are rarely effective analgesics. All the drugs tested may cause unpleasant side-effects, such as a dulling of intellectual activity, anorexia, dizziness, nausea, vomiting, and sweating. Because of the unpleasantness of these side-effects some patients cannot take morphine or its derivatives or any of the newer synthetic drugs tested. None of the drugs tested can be relied on to give analgesia without depressing the patient's alertness.

Most patients with severe pain can take large amounts of these drugs without becoming addicts; if their pain is relieved surgically they will not ask for these analgesic drugs.

I would like to thank Dr. E. A. Carmichael for his suggestions and criticisms, and Dr. Philip Ellman for providing patients for this investigation; also Dr. F. Prescott, of the Wellcome Founda-

tion Ltd., for providing supplies of amidone and blank tablets, and Drs. J. E. Page and H. M. Walker, of Glaxo Laboratories Ltd., for providing supplies of phenadoxone, Höchst 10581, and blank tablets.

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THE CONTROL OF FILARIASIS WITH HETRAZAN

A FIELD TRIAL IN A RURAL VILLAGE (KENEBA) IN THE GAMBIA

BY

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During the last three years the interrelationships and relative importance of parasitization and nutritional deficiency as factors in the causation of ill-health and low capacity for performance among Gambian villagers have been investigated by members of the M.R.C. Human Nutrition Research Unit, in collaboration with the Gambia Government Medical Department. This investigation has involved, among other things, the making of detailed surveys in the village of Keneba, in the West Kiang District of the Gambia Protectorate. The general plan of this work, and the results of the base-line survey, have already been reported (McGregor and Smith, 1952). In Keneba, after the initial surveys, measures were instituted to control or eliminate the major parasitic diseases prevalent in the area. As part of this work, an attempt was made to control filariasis on a village scale by the use of hetrazan (diethylcarbamazine). The present paper is concerned only with the results of the hetrazan trial. The general effect of control measures on health and performance of the population will be reported later. The treatment was directed primarily against microfilariae of *Wuchereria bancrofti*, but, as some of the people with this infection also carried microfilariae of *Acanthocheilonema perstans*, some information was gained concerning the effect of the drug on the latter parasite also.

Methods

Blood for enumeration of microfilariae was taken by finger-prick between the hours of 9 p.m. and midnight. It was spread thickly over a measured area of slide marked by grease pencil. The amount of blood required to cover the marked area had previously been found by measurement to be approximately 20 c.mm. It is to this volume of approximately 20 c.mm. that all microfilaria counts are referred in this paper. The thick films were dehaemoglobinized, fixed in methyl alcohol, and stained with haemalum.

The dosage of hetrazan chosen was 25 mg. base per kg. of body weight given in five equal daily doses—that is, 5 mg. per kg. daily for five days. This dosage was based on results reported by the East African Filariasis Research Unit (1950), and seemed to be the smallest dosage likely to remove most of the microfilariae permanently. Tablets of hetrazan citrate were used, each tablet containing 250 mg. of the salt, equivalent to 125 mg. of the base. One of us invariably saw that the prescribed dose was actually swallowed. The occurrence of unpleasant effects attributed to the drug was recorded and investigated, but no attempt was made to question individuals who did not themselves complain.

Incidence of Filariasis

The total population of Keneba is 710. In February, 1951, the night blood of the 603 persons present at that time in the village was examined. It was found that 118 were infected with *W. bancrofti* alone, 101 were infected with *A. perstans* alone, and 102 carried microfilariae of both parasites; thus, in all, there were 220 cases of *W. bancrofti* infection and 203 of *A. perstans*. The age and sex distribution of these infections is summarized in Table I, and has

Table I.—*Age and Sex Incidence of Filariasis in Keneba Villagers Before Treatment (February, 1951)*

Age Group (Years)	Male			Female		
	No. Examined	No. having Mf. bancrofti	No. having Mf. perstans	No. Examined	No. having Mf. bancrofti	No. having Mf. perstans
0–10	93	10 (11%)	7 (8%)	83	13 (16%)	5 (6%)
11–20	83	33 (40%)	39 (47%)	69	23 (33%)	14 (20%)
21–30	35	19 (54%)	19 (54%)	63	28 (44%)	21 (33%)
31–40	35	19 (54%)	25 (71%)	55	33 (60%)	23 (42%)
41–50	18	9 (50%)	10 (56%)	29	12 (41%)	17 (59%)
Over 50	19	9 (47%)	11 (58%)	21	12 (57%)	12 (57%)
Total	283	99 (35%)	111 (39%)	320	121 (38%)	92 (29%)

been discussed in the communication already quoted (McGregor and Smith, 1952). In the course of repeated clinical examinations during the previous year, three individuals were found suffering from elephantiasis and three had hydroceles. This gives a total incidence of such filarial sequelae of less than 1%.

It was our original intention to treat all the 220 persons found to be carrying microfilariae of *W. bancrofti*. In effect, 22 individuals were treated with another drug and 17 were not available in the village at the time the treatment was started; thus 181 persons began the course and 171 completed it. Of these, 164 were present in the village at the time of re-examination in December, 1951, 10 months after treatment, when, in all, 569 people were examined.

Results

(a) W. bancrofti.—Of the 154 infected persons who completed the prescribed course of treatment, 99 (64%) had blood free of microfilariae 10 months later (Table II). In the remaining 55 patients infection was still present, but the parasitaemia was substantially reduced; before treatment the sum of the microfilaria counts in the films of these 55 patients was 2,859, whereas 10 months later it was 305, a reduction of 89%. The overall reduction of microfilariae in the 154 infected and treated persons was 94% (5,131 in February; 305 in December). In the group of 10 cases in which treatment was incomplete and in which dosage varied from 5 to 15 mg. per kg., total elimination of microfilariae was achieved in two cases only; the remaining eight subjects showed a considerable reduction (80%)

TABLE II.—*Incidence and Density of Microfilariae in the Blood of Persons Treated with Hetrazan, Before and Ten Months After Treatment, and of Persons Untreated*

		Examination of February, 1951	Examination of December, 1951	Percentage Change
W. bancrofti. Persons present on both occasions who:				
Originally positive	(*a*) received 25 mg. per kg.			
	No.	154	154	
	No. positive	154	55	64·3% cleared
	Sum of mf. in all positive films	5,131	305	94·0% reduction
	(*b*) received 5–15 mg. per kg.			
	No.	10	10	
	No. positive	10	8	20% cleared
	Sum of mf. in all positive films	691	141	79·6 reduction
Originally negative	(*c*) received no treatment			
	No.	299	299	
	No. positive	0	26	8·7% new infections
A. perstans. Persons present on both occasions who:				
Originally positive	(*a*) received 25 mg. per kg.			
	No.	69	69	
	No. positive	69	19	72·5% cleared
	Sum of mf. in all positive films	614	51	91·7% reduction
	(*b*) received no treatment			
	No.	71	71	
	No. positive	71	48	32·4% cleared
	Sum of mf. in all positive films	402	598	48·7% increase
Originally negative	(*c*) received 25 mg. per kg.			
	No.	85	85	
	No. positive	0	11	13% new infections
	Sum of mf. in all positive films	—	19	—
	(*d*) received no treatment			
	No.	247	247	
	No. positive	0	43	17·4% new infections
	Sum of mf. in all positive films	—	145	—

in the sum of microfilariae present. Among the 299 persons found uninfected in February and untreated there were, in December, 26 new infections—8.7%.

(b) A. perstans.—One hundred and forty people carrying microfilariae of *A. perstans* in February were again examined in December. Of these, 69 had received treatment for their associated *W. bancrofti* infection; the remaining 71 had been untreated. In the treated group, 50 were found clear of microfilariae 10 months after treatment, a reduction in incidence of 72.5%. Of the 71 untreated cases 48 remained infected. In the 19 treated patients remaining infected the level of microfilarial infection was reduced from a total of 225 in February to 51 in December, a fall of 78%, whereas in the 48 untreated subjects who remained infected the sum of microfilariae rose from 318 to 598, an 89% increase. The difference between the treated and untreated groups is highly significant ($\chi^2=22.5$, $P<0.001$). New infections with microfilariae of *A. perstans*, apparent for the first time in December, were found in 11 (13%) of 85 people previously negative and treated with hetrazan, and in 43 (17.4%) of the 247 untreated persons.

Toxicity of Hetrazan

The first doses of hetrazan were accepted eagerly by the villagers, but the incidence of disagreeable side-effects was so high that their enthusiasm rapidly diminished and it became increasingly difficult to persuade the subjects to complete the course. Many who had originally presented themselves for treatment had literally to be sought out in their dwellings, and were induced to take their later doses only after lengthy debate. In spite of all efforts, eight people refused to complete the course and received one to three doses only; in two other cases treatment was discontinued because of persistent vomiting. Of the 181 persons treated, 45 (25%) complained spontaneously of unpleasant effects which were attributed to the drug, and many who did not actually complain looked unwell and miserable.

The following ill-effects were attributed to hetrazan (the figures in parentheses indicate the number of subjects affected and the percentage of the total number treated).

Headache (30=17%).—This appeared to be of general distribution. It persisted one to two days in most cases, but in eight patients it persisted throughout treatment. In most instances the heavy, stupid appearance of the sufferer suggested that the pain was of considerable severity.

Anorexia (18=10%).—This persisted throughout treatment in most cases.

Nausea (15=8%).—The duration varied from one to five days.

Vomiting (8=4.4%).—Onset variable, occurring after the first dose in some cases and in others only after the fourth or fifth dose. In three cases vomiting occurred within three minutes of the tablets being swallowed; presumably this was psychological in origin. In two instances, referred to above, the severity and persistence of vomiting were thought to justify termination of treatment.

Abdominal Pain (7=4%).—Stated by all sufferers to be severe and colicky in nature. Observation suggested that it was severe in some cases. Pain did not usually recur after subsequent doses.

Diarrhoea (4=2%).—This was mild and transient. Two of the patients reported passing ascarides.

Dizziness (3=1.7%).

Cough, Pain in Chest, and Pyrexia (5=2.8%).—In each case this syndrome appeared after the initial dose of hetrazan and was characterized by severe prostration, headache, cough, temperature rising to 103° F. (39.4° C.), and retrosternal pain, sometimes aggravated by deep breathing. Clinically the condition resembled the sudden onset of acute influenzal bronchitis. After 24 hours' rest in bed and postponement of further treatment for one day, all cases recovered completely and were able to resume their course of treatment without subsequent ill-effects. Four of the five patients had fairly heavy microfilarial infections before treatment, the actual counts being 416, 80, 75, 50, and 9 microfilariae per 20 c.mm. (approximately).

Cutaneous Eruption (1=0.6%).—One patient developed a papular rash, widely distributed over the limbs and trunk, on the fifth day of treatment. It disappeared in two days.

Localized Swellings (6=3%).—Since localized painful swellings occurring during the course of treatment may represent a change in tissue reaction at the site of an adult worm, these cases will be briefly described individually:

Case 1.—Woman aged about 26; original microfilaria count, 24. Developed painful swelling of lymph nodes of left groin after third dose of hetrazan. This was rapidly followed by considerable oedema of left leg. The patient reported that a similar swelling of the same leg had occurred seven months previously after the birth of her first child. When re-examined nine months later, the lymph nodes were enlarged but painless, and the limb was still oedematous.

Case 2.—Man aged about 65; original microfilaria count, 25. Reported painful enlargement of lymph nodes of right groin, with noticeable oedema of right foot on fifth day of treatment. Nine months later the lymph nodes were still enlarged, but were painless; the oedema was still present.

Case 3.—Man aged about 60; original microfilaria count, 9. He reported the development of a tender, painful swelling in the left groin on the third day of treatment. This swelling enlarged, softened, pointed, and five days later burst, discharging a thin purulent fluid. Twenty days after treatment the wound had healed completely.

Case 4.—Woman aged about 45; original microfilaria count, 75. She developed the syndrome of cough, chest pain, and pyrexia after the first dose of hetrazan. Next day she complained of pain in the right arm. A tender elongated mass, 5 cm. long, was palpable, lying along the medial border of the biceps muscle. The axillary lymph nodes were not enlarged or tender. This mass slowly resolved, and in three weeks had disappeared.

Case 5.—Woman aged about 35; original microfilaria count, 168. Complained of pain and swelling of left arm on fourth day of treatment. Examination revealed a tender mass, about 2 cm. in diameter, in the body of the left biceps. The axillary glands were enlarged and tender. The mass resolved completely in 14 days.

Case 6.—Woman aged about 40; lactating; original microfilaria count, 6. Developed a painful tender swelling 2½ cm. in diameter in right breast on fourth day of treatment. The mass resolved slowly and disappeared three weeks after treatment.

Discussion

Descriptions of the use of hetrazan for the treatment of hospital patients have been given by many workers and reviewed by Hawking (1950). An attempt at mass treatment of filariasis comparable to the present work was carried out by Hewitt and his collaborators (1950) in the West Indian island of St. Croix, which has a population of 12,000 to 14,000. After preliminary studies a dose of 100 mg. hetrazan citrate (that is, 50 mg. base), thrice daily for seven days, was adopted, and 10,300 "treatment units" of this amount were distributed to the population, who took it without supervision. Blood films taken from sample groups a year later indicated that the microfilaria rate had fallen by 60% from 16.6% to 6.8%, and the average microfilaria count in those remaining infected had fallen from 40 to 60 c.mm. to 4.5—that is, by 89%—the total reduction of microfilariae being 95%. A few minor toxic effects—fever, headache, and nausea—were reported, but apparently they did not cause the treatment to be unacceptable (although the amount of defaulting is unknown). Other reports on the effect of hetrazan for the long-term control of filariasis have been given by Maldonado *et al.* (1950) and Hewitt, Kenney, Chan, and Mohamed (1950).

In the present trial hetrazan (5 mg. base per kg. daily for five days) appears to have given satisfactory therapeutic results against microfilariae of *W. bancrofti*, since complete elimination was achieved in 64% of the cases, while the reservoir of microfilariae available to infect mosquitoes was reduced by 94%. These results are similar to those reported by previous workers. Although it is not known what level of microfilariaemia is needed to allow transmission to take place in the field, most of the persons still harbouring microfilariae of *W. bancrofti* 10 months after treatment contained such small numbers in the blood that it was probably difficult for mosquitoes to become infected from them. Moreover, for further propagation of the parasites to continue in a new patient it is necessary that male and female worms should meet and fertilize; unless the number of worms in the host is considerable the chances against this happening must be great. Therefore the permanent reduction of microfilariaemia to a low level, as occurred in Keneba, might well be sufficient to prevent further spread of the infection; and its final dying out might result without the achievement of complete chemotherapeutic sterilization—an end-point which requires much higher dosage of hetrazan and more prolonged treatment. Since the effects of hetrazan on the microfilaria count persist for more than 10 months it is probable that hetrazan produces a permanent effect (death or sterilization) upon the adult worms of *W. bancrofti*, although it is difficult to demonstrate such an effect in experimental *Litomosoides* infection in cotton-rats. In a few patients there were signs suggesting a cellular reaction around a dying worm—namely, localized swellings in the groin and limbs—but in most cases the death (or sterilization) of the adult worm must happen without outward manifestation.

A. perstans has usually been regarded as insensitive to hetrazan, since it is difficult to show a significant diminution of numbers of microfilariae in individual patients because of the wide fluctuations in density which occur spontaneously. In our series, however, complete elimination of microfilariae was effected in 72% of the 69 patients treated, and the sum of the microfilariae was reduced by 92%. This result suggests strongly that hetrazan exerts a considerable effect in infection by *A. perstans*, although, as the worm is not known to be pathogenic, the effect may not be of much practical importance. Since microfilariae of *A. perstans* appeared in the blood of 13% of treated subjects not previously showing infection, it is probable that the drug has no significant action upon immature developing worms.

Unfortunately, although therapeutically effective, the treatment was accompanied by unpleasant side-effects, which were more prominent and severe than those reported by other workers, with the exception of Wilson (1950) and Galliard and Mille (1949). These untoward effects may have been more disturbing because our subjects were quite unconscious of their infection and generally felt well before treatment, whereas most previous work has been done on hospital patients, who are generally not surprised at minor discomfort during their treatment. The effects may have been due to direct action of the drug (for example, nausea), to allergic reactions (fever and malaise), or to cellular reaction round a dying worm (swelling in the groin). The syndrome of cough, pain in the chest, and fever which occurred in five patients (2.8%) may have been related to the concentration of microfilariae in the lungs which occurs in the daytime as part of the microfilarial cycle (Hawking and Thurston, 1951).

This high incidence of ill-effects seriously jeopardized the success of the trial, although it was begun in most favourable circumstances. The people administering the drug were well known to the villagers, having lived and worked in the village for a year beforehand. Treatment of other diseases, such as yaws and trypanosomiasis, had established much confidence in Western medicine. Spraying of the village with BHC had enormously reduced the insect population and earned the delighted gratitude of the villagers, who altogether were in a highly receptive frame of mind. The surveys and treatment were so timed as not to interfere with agricultural activity. In spite of these exceptional initial advantages, however, it was only with the utmost difficulty that the trial was completed in face of the unpopularity of the drug occasioned by these toxic reactions. In this area the visible effects of filariasis are uncommon (less than 1%), and there is no fear of them. Consequently there is little inducement to complete a course of treatment whose ill-effects appear worse than those of the disease.

Another obstacle to mass treatment by hetrazan is the cost of the drug; this is considerable even for such a small population as that of Keneba. Unless these obstacles (unpopularity due to toxic effects, and expense) can be overcome, we are of the opinion that, at present, attempts to use hetrazan for mass treatment in areas where the people are not conscious of ill-effects from filariasis run a substantial risk of rather costly failure. On the other hand, the drug is so effective in diminishing the reservoir of microfilariae available for transmission that vigorous efforts should be made to overcome these disadvantages by diminution or different distribution of the dose or by any other possible means.

Summary

As part of an investigation into the relative importance and interrelationships of parasitization and nutrition as factors in the production of ill-health and poor performance in Gambian villagers, steps were taken to control or eradicate the major parasitic diseases,

including filariasis, in Keneba, a village of 710 population in the West Kiang District of the Gambia Protectorate.

A preliminary survey showed that of 603 persons present 220 carried microfilariae of *W. bancrofti* and 203 carried microfilariae of *A. perstans*. Treatment was directed primarily against *W. bancrofti*.

Hetrazan, in five daily doses of 5 mg. base per kg. of body weight, was administered to 181 villagers in February, 1951. Of these, 69 had microfilariae of *A. perstans* as well as of *W. bancrofti*.

Re-examination ten months after treatment showed that 64% of those treated were free of microfilariae of *W. bancrofti*, and that the total microfilariae in all those originally found infected had been reduced by 94%.

Microfilariae of *A. perstans* had been eliminated from the blood of 72% of those treated, with a 92% reduction of total load; in untreated persons the microfilariae of *A. perstans* had disappeared spontaneously in 32%, but the total microfilaria count had increased by 49%.

Unpleasant side-effects attributed to hetrazan were spontaneously reported by one-quarter of those treated. These disorders were common and severe enough to make the drug very unpopular, and it was only with great difficulty that the trial was completed, in spite of the exceptionally favourable circumstances in which it had been started.

The conclusion was reached that, in spite of the very high therapeutic efficacy of hetrazan, its common toxic effects and high cost are disadvantages which seriously prejudice the chances of its successful use for mass treatment in areas, such as this, where filarial sequelae are rare and the people have no consciousness or fear of the disease.

We gratefully acknowledge our indebtedness to Mr. D. P. Gamble, socio-anthropologist to the Gambia Government, for his invaluable co-operation; to Mr. K. Broomfield for help in examination of the blood films; to Dr. E. J. Bury, Director of Medical Services, Gambia; and to Professor B. S. Platt, Director of the M.R.C. Field Research Station, for his help and encouragement and for making the investigation possible.

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A short account of the French Prosthetic Service for the nation's war disabled is given by Lieutenant-Colonel C. Abadie, medical director of the service, in the October issue of the *Rehabilitation Bulletin* of the World Veterans Federation. Appliances are supplied at State expense so long as the patient requires them. He is free to choose his appliance among the recognized types that suit his disability. The State also pays for repairs, which are mainly carried out at workshops in the service, and for replacements when required. Amputees are entitled to two appliances, identical or dissimilar in type, for each limb amputated. In addition to appliances, severely disabled war victims may receive a hand-propelled wheel-chair of one kind or another, and the State is responsible for the upkeep and repair. A pensioner with a head wound that has led to permanent baldness has a right to a wig, which can be replaced every three years.

THE SKIN MANIFESTATIONS OF MALIGNANT DISEASE

WITH SPECIAL REFERENCE TO VASCULAR CHANGES AND DERMATOMYOSITIS*

BY

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Deposits of carcinoma in the skin usually occur late in the course of the disease. They are often few in number, and the diagnosis is established by excision and section. Of more interest to the dermatologist are the non-specific skin manifestations which can be related to the presence of a carcinoma.

When a visceral carcinoma is well advanced the skin may be pale, inelastic, and yellow in tint, without jaundice. These changes may be due to lack of appetite, diminished food intake, and difficulty in assimilation. Thus a carcinoma of the stomach or intestinal tract may interfere with iron and vitamin absorption. It is not unusual to see an atrophic dermatitis of the exposed areas of the face and arms comparable to the changes of pellagra, no doubt due to deficient intake or utilization of vitamin-B_2 complex.

Cochrane and Alexander (1951) described the case of a woman with an advanced carcinoma of the lower end of the oesophagus, who was found to have a generalized thickening and dryness of the skin, tongue, and mouth, besides numerous warts and pigmentation. With vitamin-A therapy, 700,000 units a day by mouth, "there was subjective improvement in the itching, and the skin felt much less coarse and more pliable."

As well as the nutritional deficiencies, the skin may be affected by toxic substances derived from the tumour, with degeneration of the connective tissue comparable to senile elastosis. When the liver is infiltrated the raised blood cholesterol will also contribute to the yellow colour.

Itching

The demands of rapidly growing malignant tumours on amino-acids and essential substances—for example, folic acid—may contribute to the deficiencies shown by the skin. Irritation or pruritus is the most common cutaneous symptom of malignancy, and is usually generalized. A rarity is the localized itching of the nostrils with some tumours of the brain. Itching occurs with carcinoma of the abdominal organs and of the thorax, and with Hodgkin's disease and the leukaemias. Pruritus may follow the *x*-ray treatment of an abdominal carcinoma or of a tumour elsewhere. This would suggest that a reaction comparable to a sensitization reaction occurs to protein substances released by degenerating cells. One may recall the pruritus and urticaria which have been observed following haematomata due to injury.

With the complaint of itching, inspection may reveal small, irritable, skin-coloured papules which usually disappear after the tops of the papules have been excoriated. Occasionally, however, these papules have been noted to persist, to enlarge, to ulcerate, and to display a neoplastic histology. This clinical observation has led to the suggestion that the transitory papules are an expression of a vital reaction on the part of the skin to single cells of the tumour. It is difficult not to concede that tumour cells must invade the circulation and may fail to establish themselves in the

*Lecture given at the Institute of Dermatology, St. John's Hospital for Diseases of the Skin, on January 15, 1952.

skin or be destroyed by a local mechanism, with the production of histamine-like substances with itching. If the embolized tumour cells are in larger numbers they may survive and produce a carcinomatous nodule. It is certainly true that secondary nodules are seen in the skin in only a small proportion of cases of carcinoma.

Widespread dermatitis has been encountered during the course of an advanced carcinoma. The distribution on the trunk flexures and scalp leads to the suggestion of a seborrhoeic dermatitis. The dermatitis is to be regarded as a manifestation of a deficiency, and liver by mouth or injection and vitamin-A and -B therapy are indicated.

The bullous dermatoses, including the grouped smaller blisters of dermatitis herpetiformis, have occurred with sarcoma of the thyroid (Rothman, 1925), and with a chorion carcinoma (Elliott, 1938).

Elliott's case is of interest. A woman aged 43 developed, two years after a hydatidiform mole, itching papular and vesicular lesions healing with pigmentation, and blisters on normal skin and in the mouth. The attacks seemed to be controlled with arsenic. The urine gave a positive pregnancy reaction. *X*-ray examination showed a secondary deposit in the lung. She died 27 months after her first bleeding and three months after her first cutaneous manifestations. These occurred about the time that the uterus was observed to enlarge with the increased activity of the malignant growth.

In a chorion carcinoma the increased production of hormones from the growth may be of significance in the development of the rash. The increased gonadotrophic hormone is responsible for the positive pregnancy reaction given by the urine, and it would be of interest to see if those patients with herpes gestationes which persist after delivery show evidence of similar endocrine activity.

Vascular Changes

The vascular changes which may be met with in the skin with visceral malignancy form an uncommon but dramatic group.

The localized angiomata and spider naevi when appearing suddenly in middle age have been thought to be due to a carcinoma, although any statistical evidence is lacking. Angiomata and spider naevi are to be found over the face and trunk with increasing incidence at the menopause in males and females; that is, when the incidence of carcinoma rises. Their occurrence can be related to alterations in hormone blood levels.

These spider naevi over the face and chest are common during pregnancy. In a case with well-marked telangiectasia of the face, neck, and arms, associated with each of 11 pregnancies, the dilated vessels appeared at the end of the first month of pregnancy and disappeared within five days of the delivery of a dead foetus (Forman, 1933–4). They are also met with in association with cirrhosis of the liver and pulmonary disease.

There would appear to be certain capillaries capable of hypertrophy and even of new growth, angiomata, under the influence of altered hormone levels, both of androgens and of oestrogens.

Telangiectasia

Discrete capillary dilatation over the face with more diffuse palmar telangiectasia may be found with cirrhosis of the liver and pregnancy, and also, I believe, with pulmonary disease when there is congestion of the liver. The telangiectasia is best seen over the thenar and hypothenar eminences, and the colour changes when the hands are dependent.

Bean (1943) has pictured the distribution of the palmar and digital erythema in 11 cases in his article on acquired palmar erythema and cutaneous vascular "spiders." The following case histories are of two of my patients with palmar erythema and telangiectasia of the face.

Case 1.—A gas-fitter, aged 65, in 1943 had a new growth removed from the thigh with block dissection of the lymphatic nodes, which were free of growth. The growth was said to be an "endothelioma." In 1945 he complained that he had been becoming weak and had had difficulty in swallowing. The knee-jerks were absent. The hippuric acid liver-function test was done three times, twice by the oral and once by the intravenous route. All results were low, showing diminished liver function. The patient was generally weak. He had a large number of vascular spiders peppered over his face, forehead, neck, and upper chest. They were also present on the arms, hands, and knees. There were many red angiomata (De Morgan spots) on the abdomen and thorax. A striking erythema was present on the palms in the typical distribution and on the soles of the feet. He died after having recovered from an anaesthetic given for oesophagoscopy. The essential post-mortem findings were: Heart, myocardial fibrosis. Thyroid, small and atrophic. Suprarenal glands, left, small adenomata on the surface, medulla not clearly defined; right, cortical hyperplasia. Both glands felt very firm and woody, and were of normal size. Liver smaller in size than normal; section—fibrosis present, with congestion. An enlarged mediastinal gland was sent for section and was returned as containing a deposit of oat-celled carcinoma.

Case 2.—A man aged 58 was found to have a secondary carcinoma in a rib and a (?) primary in the bronchus. While in hospital he developed spider naevi on the face and forehead and the characteristic palmar erythema, which persisted until death. Post-mortem examination showed a massive metastasis in the liver and nodules of carcinoma throughout both lungs.

The erythema of the palms resembled that described by Bean, but the considerable muscle weakness in the first case is a link with the dermatomyositis group to be described below. In both cases there was a circulatory deficiency and liver damage. The liver is known to destroy, modify, or neutralize oestrogens and androgens. The increased level of oestrogens or 17-ketosteroids due to liver disease has been held by Bean to be responsible for the telangiectasia which occurs in people with susceptible blood vessels.

Localized Erythema

Localized erythema with hyperkeratosis, resembling lupus erythematosus, has been described with carcinoma. The following case is of this type.

A man, aged 39, had in January, 1939, areas of redness and hyperkeratosis on the ears, scalp, fingers, and chest. On the chest there was an erythema with central atrophy. Small buff-coloured papules were shown at the periphery when the skin was stretched. He complained of the passage of blood and mucus from the bowel, but no carcinoma was discovered. Section of the skin showed a condensation of papillary connective tissue and capillary dilatation. One and three-quarter years after the rash appeared he died out of hospital with a diagnosis of inoperable carcinoma. No post-mortem examination was made.

A more generalized erythema with telangiectasia and atrophy has been observed with a proved carcinoma of the uterus.

A married woman, aged 68, first had erythema on the upper arms, face, and hands in March, 1946. By August there was a bright erythema of the face, eyelids, and scalp. The neck was affected where exposed to light and showed telangiectasia. The upper arms, backs of the forearms, and backs of the hands showed a fixed telangiectatic erythema with superficial atrophy, this being particularly marked on the upper arms. Over the lower lumbar region there was a small firm nodule. Biopsy of the nodule showed a cellular anaplastic tumour infiltrating freely, indicative of a high grade of malignancy (Dr. S. Navasquez). Biopsy of skin of the upper arm showed that the capillaries had surrounding oedema and lymphocytic infiltration, and the collagen bundles were separated and fragmented. Biopsy of deltoid muscle showed no myositis. In September, 1947, a carcinoma of the cervix was demonstrated.

Carcinoma Associated with Dermatomyositis

The most dramatic of the erythematous reactions in this group occurring with carcinoma are the cases of dermatomyositis. Bezecny (1935) recorded two cases in which the relationship between dermatomyositis and ovarian carcinoma was established.

A woman aged 58 had for six months had a rash which had begun with an erythema of the face, scalp, neck, and hands.

Pains in the arms and muscle weakness developed later. The musculature was affected so that she could not turn her head. The neck muscle, masseters, and the pectorals were tense and tender, and nodular infiltrations could be felt. Swallowing was difficult. The scalp and eyelids were affected and there was a diffuse alopecia. Three months later an operation was performed for large bilateral tumours of the ovaries. The surface of the ovaries and adjoining peritoneum showed carcinomatous metastases. Even a few days after the operation she was able to swallow solid food. Four months after the operation movement of the neck and swallowing had returned to normal. The facial skin was pale and there were occasional telangiectases over the temples and metacarpo-phalangeal joints.

Bezecny described a second case of a woman with an ovarian carcinoma associated with dermatomyositis. Eleven days after the operation there was great improvement in the skin and muscles.

The following three cases, personally observed, are examples of this association :

A woman aged 60 years had an inoperable carcinoma of the breast and developed erythema of the back, the backs of the hands and fingers, the extensor aspects of the forearms, and the ankles. There was also definite weakness of the shoulder muscles. The erythema faded after two months, leaving atrophy and pigmentation.

A woman aged 51 years had a gland removed from the left side of the neck in July, 1937. This was found to contain a squamous-cell carcinoma. It was suggested that the primary was in the lower oesophagus, but this was never proved. In October, 1937, she developed an erythema of the face, ears, and hands. She had been given deep *x*-ray treatment. When seen in December, 1937, she had developed weakness of the shoulder-girdle muscles and difficulty in speech and swallowing. Over the whole face, neck, shoulders, and front of the chest the skin was erythematous and cyanotic, particularly over the eyelids, and there was an erythema over the forearms and backs of the hands. Subsequently the erythema faded and the weakness of her shoulders improved. Her general condition deteriorated, however, and she developed a mass in the pelvis, probably secondary deposits. A few months later she died. Section of the skin and deltoid muscle showed a thin epidermis, oedema, and fragmentation of the collagen bundles. The muscle bundles were atrophied and tortuous, with multiplication of the sarcolemmal nuclei.

A man aged 62 years had had a partial gastrectomy for a gastric carcinoma a year previously. Six months later he developed an erythema of the face, swelling of the eyelids, and erythema of the hands and forearms. A month later there was loss of hair, difficulty of speech and swallowing, and weakness of the shoulder-girdle and buttock muscles. Shortly before he was seen there had been a recovery of power, swallowing had become possible, and the erythema had faded. There was considerable wasting of the shoulder muscles, the skin of the face and orbits was telangiectatic and pigmented, and similar changes were noted on the back of the neck, shoulders, and buttocks. Subsequently he developed a painless obstructive jaundice.

Acanthosis Nigricans

Lastly, reference may be made to the proliferative epithelial changes known as acanthosis nigricans, the association of which with carcinoma of the abdominal viscera or of the bronchus has been found in a high proportion of cases over the age of 40. Even in cases under 30 years the prognosis must be reserved. The hypertrophy affects the skin, particularly of the flexures, and mucous membranes. The cases in which there is no malignancy tend to pigment less, and most of them occur in the years of puberty.

An interesting case of a girl aged 13 with acanthosis nigricans was recorded by Watson Smith (1933). The skeleton was overdeveloped, with a large jaw, hands, and feet. her height was 5 ft. 11 in. (180 cm.) and her weight 11 st. 4 lb. (71.7 kg.). She grew a profuse beard of fine lanugo hairs and her arms and legs were unusually hairy. There was thus evidence of anterior pituitary and adrenocortical overactivity. Kok (1951) recorded an interesting case of acanthosis nigricans in a patient with cirrhosis of the liver and discussed the role of the consequent metabolic and endocrine changes.

Discussion

In the above account of the erythematous and telangiectatic changes evidence is given of parallel manifestations due to endocrine changes—for example, in pregnancy and the menopause—and to liver dysfunction. One must consider whether there is a similar alteration in hormonal blood levels in those cases of erythema, telangiectasia, and dermatomyositis occurring during the course of a carcinoma. Further, there is a possibility that a period of altered hormone levels may be a factor potentiating or activating a carcinoma. Certain work may be mentioned in support of this view.

Thus oestrogens injected into certain strains of male rats give rise to carcinoma of the breast, and in female mice to carcinoma of the uterus (Payling Wright, 1950). Chemical substances with a structure similar to hormone steroids—for example, anthracene—when given by mouth in rats produce carcinoma of the lungs. The incidence of the induced carcinoma was of statistical importance (Payling Wright, 1950). The common carcinomata in women are those affecting the breast, uterus, and ovaries—structures which are particularly sensitive to hormonal effects. A myopathy with muscle changes similar to those of dermatomyositis has been recognized in some cases of hyperthyroidism.

However, the telangiectatic element of the cutaneous reaction would be expected to appear early in the course of a neoplasm if the latter were induced by endocrine changes. In the above cases in which blood vessels, connective tissue, and muscles were involved, the signs appeared late in the course of the malignancy.

One must therefore assume that if altered hormone levels are of importance in these vascular, connective tissue, and muscle changes, these occur during the course of a neoplasm for the following reasons: (*a*) malignant invasion of the liver, disturbing its regulating function on hormone blood levels; (*b*) carcinomatous tissue itself may produce a chemical substance with an effect on blood vessels and connective tissue (Bezecny, 1935); and (*c*) certain carcinomata —for example, ovarian carcinoma—may themselves produce hormone steroids or may induce altered pituitary activity.

Summary

The " cachectic " skin is observed particularly in relation to malignant disease of the gastro-intestinal canal. The skin is dry, inelastic, scaly, pale, and yellow.

These changes are due in part to disturbance of digestion and absorption of iron, protein, and accessory food substances. The yellow tint may be in part due to degenerative changes in connective and elastic tissue. These deficiencies may occasionally lead to a chronic dermatitis.

Pruritus is a frequent symptom of carcinomas, reticuloses, and leukaemias. The suggestion is made that this is due to a sensitization to the altered protein of the malignant tissue or possibly follows on the destruction of malignant cells in the skin.

The rare bullous reactions, resembling dermatitis herpetiformis or pemphigus, may be caused by a similar mechanism. Dilatation of the capillaries—localized as spider naevi or angiomata, or diffuse telangiectasia of the palms and soles—has been observed with carcinoma.

Again localized capillary dilatation and alteration in the connective tissue, leading to clinical changes resembling lupus erythematosus and scleroderma, forms a link between simple telangiectasia and dermatomyositis occurring with carcinoma.

Consideration has been given to the possible role of hormones in the aetiology of the vascular dilatation and mesoblastic tissue degeneration. Thus alterations

of hormone levels with pregnancy may explain the telangiectasia of the face and chest, reversible after parturition.

Disease of the liver, with disturbance of its ability to regulate oestrogen and androgen blood levels, has been known to be associated with telangiectasia of the face and palms, and occasionally with enlargement of the male breasts.

A myositis may be an early sign of thyrotoxicosis.

At some stage in their course malignant tumours of the genital organs—for example, the ovaries—may themselves produce steroids capable of affecting vessels and connective tissue.

Acanthosis nigricans in which there is hypertrophy and pigmentation of the skin, in adults, is in most cases associated with malignancy. The maximum incidence of the benign cases is at puberty, and in one case quoted there was additional evidence of endocrine disturbance (acromegaly and virilism).

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EFFECTS ON FOETAL WEIGHT OF GROWTH-HORMONE-CONTAINING ANTERIOR PITUITARY EXTRACTS GIVEN TO PREGNANT RATS

BY

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It has long been recognized that pregnancy in women suffering from diabetes mellitus is associated with a high foetal mortality rate and the tendency to foetal gigantism. It is now well known that pregnancy in women who subsequently develop diabetes mellitus is also associated with these features, but in lesser degree (Miller *et al.*, 1944; Miller, 1945; Henley, 1947; Barns and Morgans, 1948; Gilbert and Dunlop, 1949; Gilbert, 1949). This pre-diabetic phase is probably of some fifteen years' duration (Barns and Morgans, 1948).

It has been suggested that excessive production of the diabetogenic-growth hormone by the maternal anterior pituitary gland may be responsible for the large foetuses in pre-diabetic and diabetic pregnancies and also for the subsequent development of the diabetic syndrome in the pre-diabetic woman (Barns and Morgans, 1948; Gilbert, 1949). Further, the overactivity of the maternal anterior pituitary gland may be responsible for the high foetal mortality rate (Barns and Morgans, 1948). Experimental studies in rats suggested the possibility that excess of the diabetogenic-growth complex itself may be the factor responsible for the foetal deaths (Barns *et al.*, 1950).

The present investigation has been undertaken to see whether there is any experimental support for the suggestion that an excess of the diabetogenic-growth factor causes foetal gigantism. In it we have studied the effects on the foetal weights of injecting pregnant rats with anterior pituitary extracts containing the diabetogenic-growth complex. The rat in such circumstances might reasonably be regarded as being in the "pre-diabetic state," although it must be pointed out that it is not possible to induce diabetes in this species by such injections (Young, 1938).

Experimental

Virgin adult female rats of mixed strains weighing 120–210 g. were used for the experiments recorded. They were put with bucks, and the finding of the "placental sign" (vaginal bleeding at about the 14th day of pregnancy) was adopted as a sign of conception. Subcutaneous injections were begun on the day of finding the placental sign and were given daily until the 20th day of pregnancy, when the animal was killed and the live foetuses were weighed. In each series of experiments control animals were treated similarly but were not injected. The fractionated anterior pituitary extract (fractionated A.P.E.) used was a "saline supernatant" fraction prepared by isoelectric precipitation from crude A.P.E. obtained from fresh ox anterior pituitary glands (Reid and Young, 1948; Reid, 1949). Two-thirds of the protein in this preparation consists of growth hormone, and it is possible that traces of other hormones present in the fraction are a constituent part of the diabetogenic-growth complex. The fractionated A.P.E. was unlikely to contain gonadotrophins in appreciable amounts, and tests carried out by three methods of assay failed to reveal their presence (Barns *et al.*, 1950).

Growth hormone (Armour and Co., J-21609R) was kindly supplied by the makers. Experiments were performed with this preparation to verify its activity, and the results clearly demonstrated its growth-promoting properties (Barns and Swyer, 1951). All the rats were weighed daily from the time of finding the placental sign. They were kept at 72° F. (22.2° C.), and were fed a vitamin-enriched cube diet *ad lib.*

Results

Controls.—Previous experiments (Barns *et al.*, 1950) had shown that saline injections and injections of liver extract had no effect on pregnancy in the rat; therefore no injections were given to the control animals. There were 35 pregnancies in the control group; seven of these were excluded from the series either because of early delivery or because of abnormality of the pregnancy such as uterine bleeding. Of the remaining 28 pregnant rats, 19 were killed on the 20th day of the pregnancy (corresponding with the fractionated A.P.E. experiment) and 9 on the 21st day of the pregnancy (corresponding with the growth-hormone experiment). From the former group of 19 controls there were 161 live foetuses and from the latter group 91. Further statistical details are shown in the table.

Fractionated A.P.E.—Eleven pregnant rats were injected with fractionated A.P.E. (0.5 ml. daily, corresponding in diabetogenic potency to 0.4 ml. of crude A.P.E. and to 1.2–2 mg. approximately of growth hormone); five of these rats were excluded from the series because some dead foetuses were found *in utero* when the animals were killed on the 20th day. The remaining six pregnancies produced 47 live foetuses. A further nine pregnant rats were injected with 0.3 ml. daily; two of these were excluded, one on account of early delivery and the other because of intrauterine death. The remaining seven pregnancies produced 36 live foetuses. Because the total numbers were small it

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was felt justified to combine the figures for the two groups, and we thus obtained 13 pregnancies which produced 83 live foetuses (see Table).

Effects of Injections of Fractionated A.P.E. and of Growth Hormone on Litter Size and Foetal Weight

Group		No. of Litters	Mean Litter Size and Standard Error	Mean Foetal Weight (g.) and Standard Error	Correlation of Foetal Weight and Litter Size
A.P.E. (killed on 20th day)	Control	19	8·474±0·421	2·984±0·249	−0·605
	Treated	13	6·385±0·813	4·117±0·267	−0·670
Growth hormone (killed on 21st day)	Control	9	10·111±0·807	4·138±0·206	+0·481
	Treated	7	8·714±0·944	4·877±0·198	−0·461

Growth Hormone.—Ten pregnant rats were given a daily dose of 1 mg. of growth hormone; three were discarded from the series owing to early delivery or intrauterine death. The remaining seven pregnant rats were killed on the 21st day of pregnancy and produced 61 live foetuses (see Table).

The table gives the mean litter size and mean foetal weight (together with their respective standard errors) for the various groups mentioned above. From these figures it may be concluded that the mean foetal weight of the rats treated with fractionated A.P.E. (the pregnancy being terminated on the 20th day) is significantly greater than those of corresponding controls ($t=3.034$, $n=30$, $P=0.005$). It also appears that the mean litter size of these rats is significantly less than that of the corresponding controls ($t=2.444$, $n=44$, $P=0.019$). However, since there is a significant correlation between foetal weight and litter size it is possible that the difference in the mean foetal weights could be due to the difference in the litter sizes. If we correct the foetal weights of both controls and treated groups for the difference in the litter size (using the mean value of the correlation for 20 days) it is found that the difference between the corrected mean foetal weights in the two groups ceases to be significant ($t=1.884$, $n=29$, $P=0.067$). It will be noticed, however, that this difference is only just short of significance at the 95% probability level.

In the case of the rats treated with growth hormone and killed on the 21st day of pregnancy, the mean foetal weight is again significantly greater than that of the corresponding controls ($t=2.530$, $n=14$, $P=0.024$). In this experiment, however, there is no significant difference in the mean litter size of the two groups ($t=1.167$, $n=44$, $P=0.256$). Furthermore no clear correlation between foetal weight and litter size exists either for the controls or for the treated animals. The explanation for this unexpected finding is not forthcoming. It is possible, though doubtful, that seasonal variation could account for this, because the experiment with fractionated A.P.E. and its corresponding controls was carried out at a different time of the year from that with growth hormone and its corresponding controls. It will be noticed that in both experiments the controls have a smaller mean foetal weight and a larger mean litter size than the corresponding treated animals. If it were thought justifiable to use the correlation obtained for the 20-day group in order to correct for the differences in litter sizes rather than the doubtful correlation values obtained for the 21-day group, then it would be found that the corrected mean foetal weight for the animals treated with growth hormone is not significantly different from that of the corresponding controls.

Discussion

Prolongation of the pregnancy in rats has been shown to produce enlargement of the foetus. This post-maturity has been produced by injecting the mother rat with alkaline extracts of anterior pituitary lobe (Teel, 1926; Hain, 1932). Sontag and Munson (1934) obtained large foetuses in rats, using growth hormone of the anterior pituitary gland ("antuitrin G"). In this case the enlargement was also thought to be due to prolongation of the pregnancy. In each of these investigations a number of stillbirths was obtained. Watts (1935) injected pregnant rats with preparations of growth hormone of the anterior pituitary gland and obtained large offspring without post-maturity. With some preparations, however, she also obtained prolongation of the pregnancy and usually stillbirths. She noted a significant increase in the maternal weight of the injected rats.

We have also obtained an increase in the weight of the mother animal treated with anterior pituitary extracts during pregnancy (Barns *et al.*, 1949). It is not possible to make the rat diabetic or to produce glycosuria by injections of the diabetogenic-growth complex; while receiving such treatment the rat reacts similarly to puppies in that an increase in weight is the principal effect (Young, 1945). It would therefore seem justifiable to assume that part of the injected diabetogenic-growth factor is utilized to cause this increase in growth rate of the mother animal, and that correspondingly less would be available for increasing the growth of the foetus. Clearly our results do not provide unequivocal evidence of increase of foetal weight under the influence of growth-hormone treatment; for in the case of A.P.E. significant reduction of litter size could itself have accounted for the larger foetus; while when growth hormone was used, the litters, though not significantly smaller, were certainly not as large as those of the controls. Our previous experiments with A.P.E. (Barns *et al.*, 1950) had already indicated its lethal effect on the foetus, and in the present experiments it will be recalled that when macerated foetuses were found *in utero* the litter was excluded. In addition to these late intrauterine deaths it would seem that earlier foetal death with complete resorption must have occurred in some of the injected animals, and so account for the observed smaller litters.

It is unfortunate that the number of experimental animals has been too small to enable us to obtain a definite answer to the question of whether an excess of the diabetogenic growth hormone could account for foetal gigantism. Limitation of the supply of hormone preparations at our disposal made this inevitable. It might be that had this experiment been carried out on a larger scale a more clear-cut result would have been obtained.

Grateful thanks are due to Professor F. G. Young and Dr. E. Reid for supplies of fractionated A.P.E.; to Dr. Irby Bunding, of Armour and Co. Inc., for supplies of growth hormone; and to Mr. N. W. Please, of the Department of Statistics of University College, London, for kindly undertaking the statistical analysis.

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A health insurance scheme for all was proposed to the President's Commission on the Health Needs of the Nation at its hearing in Washington on October 7 (*New York Times*). As outlined by a director of the Chicago Commission on Financing of Hospital Care, wage-earners would "prepay" medical care from diagnosis to the end of treatment. The rest of the population would be handled by categories—for instance, for the unemployed, hospital and medical care prepayments might be tied to unemployment insurance. The hearing was marked by a controversy revolving around Frank G. Dickinson, an economist of the American Medical Association. Mr. Dickinson's leading charge was that the "fact book" issued by the group was devoted more to cost than to the quantity and quality of medical care.

NERVOUS SIGNS IN SARCOIDOSIS

BY

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The occurrence of neurological complications in sarcoidosis, though well established in the literature of the disease, is a fact perhaps still not very widely known. The signs most commonly met are those of lesions of cranial or peripheral nerves. Without any doubt the most frequent disturbance is paralysis of the facial nerve, but retrobulbar neuritis, papillitis, optic atrophy, cycloplegia, ptosis, external ocular palsies of one kind and another, trigeminal sensory loss, nerve deafness, weakness or paralysis of the palate or pharynx or of the vocal cords or tongue, loss of taste, or anosmia, are all more or less often encountered, and so too are motor, sensory, and reflex signs and symptoms, of nerve or root type, in the limbs and trunk. Any of these disorders may occur in isolation, or may be combined with others to present as a multiple neuritis. Rather less often there may be evidence of central nervous dysfunction, usually alone but sometimes in conjunction with peripheral lesions. Focal or generalized fits, hemiplegia, confusion, coma, extrapyramidal syndromes, cerebellar disorders, and symptoms indicating mischief in the brain stem or spinal cord have all been reported. In particular, diabetes insipidus from hypothalamic or pituitary damage has been recorded a number of times. Lastly, symptoms of meningeal involvement are occasionally seen, with headache, neck stiffness, a raised cerebrospinal fluid protein content and white-cell count, and sometimes reduction of the sugar and chloride content.

The four case records which follow are presented to exemplify some of these features: the first two patients had polyneuritic syndromes, the next a spinal cord disorder, and the fourth a combination of central and peripheral nervous lesions.

Case 1

A married woman aged 29, a patient of Dr. Ernest Bulmer, who kindly allowed me to see her, became ill just before Christmas, 1950, with bilateral swelling of the parotid glands, at first thought to be mumps. However, the swelling did not subside, and after six weeks severe iridocyclitis of both eyes supervened. It became clear that she was in fact suffering from the uveoparotid form of sarcoid, first described by Heerfordt in 1909.* Her eyes remained inflamed and her sight dim for about eight weeks, and the parotids were swollen for some four months in all. During this time she felt ill, with lack of energy, poor appetite, and dry mouth, and lost weight steadily at the rate of 1 to 2 lb. (450 to 900 g.) a week. She observed of her own accord (because they were tender to the touch) that the lymph nodes in various parts of her body were enlarged, and a chest *x*-ray film showed that the typical radiological signs of pulmonary sarcoid were also present.

In April, 1951, she had the first of what proved to be a series of neurological symptoms, which came on in turn until mid-August. The initial complaint was drooping of the left upper eyelid and fixed dilatation of the left pupil, which made it difficult to focus near objects with that eye. At the beginning of May she had diplopia, and a little later the left side of her face and inside of the mouth became numb. In early June pain developed in the left leg, and with its onset she became aware of constant tingling in the front of the thigh and shin, and a tendency for the limb to give way when walking. More or less simultaneously pain started in the left arm down its outer side from shoulder to mid-forearm level, and the hand felt constantly cold. At this time too the right axilla felt numb and dead for a short while. A few weeks later, at the end of June, the right arm and leg were affected with rather similar symptoms, which came on (she said) very abruptly in the space of about three hours. In July the skin over the right lower ribs felt frozen, and, finally, on August 12 she woke to find the right side of her face paralysed.

During the period of evolution of her nervous troubles she had first a fine nodular eruption on her forehead, which had apparently been more palpable than visible, and then crops of purplish-red lesions on the shins and extensor aspect of the forearms, which she likened to chilblains. Her family and social history and her previous medical record were blameless.

On examination (August 17) she was haggard and thin, her weight being nearly 3 st. (19 kg.) below its normal level. There were no clinical signs in the chest, the liver and spleen were not enlarged, and only a few small glands were palpable in the right supraclavicular fossa and in both groins. The salivary and lacrimal glands were not swollen, nor was there any sign of uveitis. The various skin eruptions of which she had complained had vanished, leaving no trace beyond some shiny pigmented patches, desquamating at their edges, over both tibiae. The salient neurological features were as follows: the left pupil was widely dilated and immobile, the right rather smaller and responding sluggishly to light and on convergence. There was bilateral ptosis, slight but definite on the right and obvious on the left, and diplopia in all directions of gaze, especially to the sides, without visible fault in eye movements. There was somewhat impaired touch and pain sense in all divisions of the left trigeminal nerve, most marked in the third, and the corneal reflex was depressed. Complete right facial palsy of lower motor neurone type was present. In the arms there was slight blunting of sensory acuity of root pattern, from the eighth cervical to the second thoracic dermatome on the right, and in the territory of the fifth and sixth cervical dermatomes on the left. Both legs were a little weak, the left slightly worse than the right; the left knee-jerk was greatly diminished, and the ankle-jerks were both absent. There was mild objective numbness from the fourth lumbar to the first sacral root inclusive in the right leg, and in the left from the second to fifth lumbar root.

I saw her again on October 15. She had made a great symptomatic improvement, and was scarcely recognizable as the same person. Her only spontaneous complaint now was of shock-like paraesthesia in the arms and legs, mostly at night, which made her limbs jump. The facial palsy had largely but not completely recovered, and her other signs had also become much less easily demonstrable.

Case 2

A 47-year-old widow was taken ill early in December, 1945, with a vague febrile malaise. Two or three weeks later her fingers gradually went numb one by one, starting with the middle finger of the left hand, and the grip of both hands became weak. Soon afterwards a constant tight feeling round the lower ribs came on, more on the left side than on the right, with recurrent girdle pains. She discovered that the skin felt peculiar and uncomfortable, if she touched it or her clothes rubbed it, in a band on either side from ribs to navel. The power in her legs became increasingly disturbed till she could scarcely walk or stand, and both big toes became numb. She also had intermittent pains in both arms and legs. These symptoms took some weeks to evolve, remained at full intensity for a further few weeks, and then slowly receded. They were already

*It is now generally recognized that uveoparotitis is simply a phase or variant of sarcoidosis (Bruins Slot, 1936; Longcope and Pierson, 1937; Bruins Slot *et al.*, 1938; Sandbacka-Holmström, 1940; Roos, 1940).

beginning to recover somewhat, when, in April, 1946, the sight in the right eye became dim and foggy; a fortnight later the left followed suit. On May 24 she was admitted to the Queen Elizabeth Hospital under the care of Professor P. C. P. Cloake. Examination at this time showed bilateral diffuse uveitis, with posterior synechiae, keratic precipitates, and vitreous haze—findings which accounted for the depression of her visual acuity. The pupils were dilated and fixed, the right slightly larger than the left, there was impaired sensation in the finger-tips of both hands and on the trunk in the distribution of the seventh to the ninth thoracic segments, and diffuse weakness of both legs of moderate severity. The arm-jerks were diminished, the knee-jerks very weak, and the ankle-jerks absent. The other systems were clinically normal.

A chest *x*-ray film showed increased hilar shadows with fine reticulation of the parenchyma, and serum protein estimation a relative increase of the globulin fraction, though the total was not definitely increased. A Mantoux test was negative at 1:1,000. C.S.F. examination gave a normal fluid with three lymphocytes per c.mm., 26 mg. of protein per 100 ml., negative Pandy test and Nonne–Apelt reaction, and Lange curve 0011000000. The C.S.F. and blood W.R. were both negative.

The patient was in hospital about five weeks, during which time she made rapid progress towards recovery. Ever since then she had been kept under observation as an outpatient. I saw her on September 6, 1951. She said that it was 12 to 18 months after the onset of her illness before she felt really well, but in the past four years her health had been good. Her only complaints were of occasional tight feelings round the trunk and sometimes of faint numbness in the finger-tips. Nothing significant could be discovered in her previous medical, social, or family history. On examination the pupils were still unequal and moderately dilated, and almost completely inactive to light and on convergence. The triceps-jerks and all the leg-jerks were still absent, and there was still a demonstrable band of hyperaesthesia on the trunk in the same distribution as before, though no abnormality could be found in the finger-tips even with two-point testing. The chest *x*-ray picture was now perfectly normal, and the plasma proteins were normal in total and ratio.

Case 3

A 39-year-old joiner sought medical advice in 1944 on account of chronic cough, with sputum occasionally blood-stained, and shortness of breath on exertion. He was at first suspected of having phthisis, but in 1948 a generalized enlargement of lymph nodes and an enlarged liver and spleen were discovered. Lymph node biopsy was then carried out, which showed the characteristic histological features of sarcoid. From 1948 onwards he had had recurrent inflammation of the eyes of variable duration, one attack of apparently simple pneumonia, and a transitory swelling of the left testicle, which lasted about eight weeks. His nervous complaints dated from April, 1950, when he noticed that his feet and legs felt continuously cold, and that their strength was beginning to fail a little. The enfeeblement of his legs progressed, and it was gradually borne in on him that feeling was blunted not only in the legs but on the trunk up to about waist level, and his sphincters became difficult to control.

On December 5, 1950, he was admitted to the neurosurgical unit of the Queen Elizabeth Hospital under Mr. J. M. Small. I saw him a few days later. Neurological examination then demonstrated a profound spastic paraplegia, with cutaneous sensory loss in the trunk and lower limbs, the upper border of which was at about the sixth thoracic segment on each side, and gross defect of postural and vibration sense. The signs were essentially those of a central cord lesion. General examination revealed moist sounds in both lungs, palpable liver and spleen, mild widespread lymphadenitis, bilateral chronic phlyctenular conjunctivitis, and a curious rash round the mouth and over the lower jaw, consisting of many closely placed flat-topped yellowish little papules set upon an erythematous background.

Various investigations were made. Chest *x*-ray examination demonstrated a heavy fibrosis of both lungs. The sputum was negative for tubercle bacilli on several occasions, the Mantoux reaction was negative, and the serum proteins were normal. A full blood count was normal, but the E.S.R. (Wintrobe) was 28 mm./hour. The C.S.F. protein was elevated (236 mg. per 100 ml.). C.S.F. and blood W.R. were both negative. Myelography was quite normal, and a diagnosis of a sarcoid lesion in the mid-thoracic segment of the spinal cord was made.

Through the kindness of Dr. I. Gallant, the patient was seen again at St. Chad's Hospital, Birmingham, early in October, 1951. There was little change in his neurological or general physical state. His legs were spastic, and, except for a flicker of movement in the toes, completely paralysed. There was knee and ankle clonus with briskly upgoing toes. Postural and vibration sense were grossly disturbed in the lower limbs, and there was still a sensory level for touch, pain and temperature at the sixth thoracic dermatome, with relative escape of the sacral segments bilaterally. The arm-jerks were somewhat exalted on both sides, a finding which had been noted the previous December, but otherwise the arms and cranial nerves were normal.

Case 4

A housewife aged 41 was first admitted to the Queen Elizabeth Hospital under Professor W. H. Wynn on May 25, 1944. She then gave a history of having had Bazin's disease of the legs from the age of 14 until she was 35. Two years before admission to hospital she had developed a cough with sputum, and had begun to lose weight steadily and to feel unwell. Twelve months later her hands and feet had been numb for some time, and since then recurrent small lumps had appeared in the skin of the face and limbs. For six months she had been excessively thirsty and had to pass urine very often.

On examination she was thin, being some 2½ st. (15.9 kg.) underweight. There were numerous old ulcer scars on both legs, relics of her earlier erythema induratum, palpable glands in the axillae, an easily palpable spleen, moist sounds in both lungs, and slight hypertension (B.P. 170/100). There were also some small raised rose-red lumps 1 to 1.5 cm. in diameter on both forearms, and a slight but definite weakness of the left side of the face of peripheral type with deviation of the tongue to the left on protrusion. The chest *x*-ray picture showed a little hilar enlargement and bilateral basal fibrosis. The serum proteins were normal. She was observed to have an irregular low fever, and it was confirmed that her fluid intake and output were abnormally high. A diagnosis of sarcoidosis with diabetes insipidus from hypothalamic involvement was made, and the patient was sent out of hospital on June 10.

On August 3 she was readmitted, complaining that since going home her limbs had become stiff and weak, and her gait restricted, and that one week previously the right side of her face had become paralysed. On examination there was complete infranuclear palsy of the right seventh nerve, but the other cranial nerve signs previously described had gone. There was some weakness of the arms and legs, with rather variable spasticity, increased tendon-jerks, and extensor plantar reflexes, but no objective sensory disturbances. In less than a month the facial palsy had almost completely recovered, and the signs of spinal cord dysfunction were thought to have diminished. Treatment with pituitrin snuff controlled the patient's diabetes insipidus very satisfactorily, and she was sent home on this drug.

On September 26, 1945, she was admitted for a third time with complaints of lassitude, intermittent pains in the limbs, and twitching of the legs. There were no cranial nerve signs, but a mild spastic tetraparesis was still evident, with flexor spasms in the legs. General physical examination was essentially as before. The C.S.F. protein and cell count

were normal, also the Lange curve. The C.S.F. and blood Wassermann reactions were negative. A chest *x*-ray film showed increased basal lung markings as before, and the serum protein ratio was now abnormal (albumin 3.5 g., globulin 3.3 g.).

She was again in hospital in the summer of 1946, under Dr. J. M. Malins. She now had to use a stick to get about even in her own home. Six months previously she had had bilateral uveitis, which recovered slowly, and a week before admission a left peripheral seventh-nerve paralysis had come on. The pyramidal signs in her limbs were unchanged or perhaps a little more severe. In April, 1947, when examined once more in hospital, the liver and spleen were both easily palpable, there were firm glands in the neck and armpits, and a fading sarcoid lesion of the skin on the right wrist and another over the proximal phalanx of the right middle finger; her blood pressure had risen to 185/105. Neurologically she was *in statu quo* so far as her limbs were concerned; the left facial palsy had made only imperfect recovery, and the right pupil was now dilated and fixed. *X*-ray films of the hands showed no sign of osteitis multiplex cystica. The sedimentation rate was 20 mm./hour (corrected). Serum proteins: albumin 3.7 g., globulin 3.8 g.

Six months later she was in congestive heart failure, and while being treated developed occlusion of the popliteal artery, which necessitated amputation of her left leg below the knee. A year later (November, 1948) she had to be treated, again in hospital, for heart failure; her neurological signs were stationary. In January, 1949, she was transferred to a home for incurables, and her subsequent history is unknown.

Comment on Cases

In contrast to Case 1, in which nervous derangements appeared only at a relatively late stage, Case 2 actually presented with a neurological symptomatology.

Cases 1 and 2 are perfectly typical in their course and symptomatology of polyneuritic sarcoid, and can be matched by a score or more of published examples. Case 3, on the other hand, is one of sarcoid involvement of the central nervous system.

In the context of Case 3 it may be remarked that the prognosis for recovery of nervous function is very much better with peripheral than with central lesions, a point which is also attested by Case 4, in which the spinal cord signs showed little or no improvement, though there was recovery from more than one attack of infranuclear facial palsy. The notes on Case 4 were taken from the records of the Queen Elizabeth Hospital, and this patient never came under my observation at any stage of her illness.

In Case 4 there were signs and symptoms of both peripheral and central nervous involvement, as witnessed by the recurrent facial palsies of lower motor neurone type and spastic tetraparesis; the diabetes insipidus which was a prominent feature at one stage was presumably caused by a sarcoid deposit either in the hypothalamus or in the pituitary itself. The early history of Bazin's disease suggests the possibility that the latter may be a form of cutaneous sarcoid: descriptions of the histology of the lesions of erythema induratum are not contrary to such a view.

Discussion

A reading of the more easily available literature on sarcoidosis suggests that the incidence of nervous complaints in the uveoparotid form of the disease is so high that it constitutes an almost regular feature of the syndrome. All three of the cases upon which Heerfordt (1909) based his original account of "subchronic uveoparotid fever" had such troubles: the first (a boy of 11) had optic neuritis; the second (a boy of 14) facial palsy and difficulty in swallowing; and the third (a man of 27) facial palsy, difficulty in swallowing, and sensory upset in hands and trunk. He cited from earlier writers two further cases, which he grouped with his own: one had facial paralysis and loss of taste in one-half of the tongue and the other retrobulbar neuritis. Other examples with a wide variety of complications—mainly polyneuritic—were later published by numerous observers (Mackay, 1917; Maitland Ramsay, 1921; Feiling and Viner, 1921–2; Macbride, 1923; Critchley and Phillips, 1924; Parker, 1926; Rogers and Bodman, 1926; Merrill and Oaks, 1931; Mohn, 1933; Garland and Thomson, 1933, 1934; Lloyd Davies, 1934; Savin, 1934; Tait, 1934; Levin, 1935; Waldenström, 1937; Bruins Slot *et al.*, 1938).

On the other hand, nervous symptomatology in the Boeck–Schaumann variants seems to be a relative rarity. Thus Bodley Scott (1938) described eight cases, none of which had nervous signs; and Longscope (1941), who published observations derived from experience with 31 cases, had met them very seldom. Their absence is also a striking feature of Alsop Riley's (1950) series of 52 personal cases. According to Salvesen (1935), who reported a patient with optic neuritis, nervous lesions had previously been observed only by Winkler in 1905, by Mazza in 1908, by Urban in 1910, and once by Boeck himself (who was, however, inclined to regard his case as due to coincident leprosy). Schaumann (1936) made passing reference to sarcoid lesions in the nervous system as an infrequent part of the disease. In the past 10 to 15 years a number of further case descriptions have accumulated (Roos, 1937; Bruins Slot *et al.*, 1938; Lindau and Löwegren, 1940; Colover, 1948; Williams, 1950). It would appear, therefore, that there is a differential frequency of occurrence of nervous signs within the group of sarcoid disorders which would bear further investigation. It is possible that the difference may be no more than the result of a bias in medical reporting, but, at least superficially, it seems too large to be thus explained away.

With regard to pathology, neurological symptoms are caused by the presence in the neural substance of epithelioid and giant-cell follicles without caseation, just like those found in other tissues. How the lesions come to be present in the nervous system is a point which deserves brief consideration. Schaumann (1936), who did much to unify the diverse clinical manifestations of sarcoid, always insisted that it was primarily and electively a system disease, an affection of the reticulo-endothelial system, and it is now generally accepted as a reticulosis. The primitive mesenchymal cells of Maximow, which (as in other reticuloses) are the target of attack, are present in every tissue of the body, though more richly in some than in others, and it is their proliferation and differentiation which gives rise to the characteristic lesions. Sarcoid follicular systems in the cerebrospinal axis are thus to be looked upon simply as a sign of local reaction by indigenous mesenchymal cells, part and parcel of a widespread reticular response to whatever is the cause of the disease.

What the aetiology of sarcoidosis may be is still unknown. In the past there has been much discussion of its relationship to infection with the tubercle bacillus. It has been postulated that it is the result of an anomalous response (anergy) on the part of the host's tissues to invasion by the organism, or that the organism itself is of attenuated virulence, or that both factors act simultaneously. However, no really satisfactory proof of the causal nature of Koch's bacillus has ever been given. Though it seems that in something like 10% of cases frank tuberculosis—for example, pulmonary, renal, or meningeal—is either the immediate or a contributory cause of death, a similar incidence is to be met with in other conditions, such as Hodgkin's disease or silicosis. In each instance the coincidence of the primary illness with tuberculosis can more easily be interpreted as meaning that the former predisposes the subject to infection with the latter than to suppose that tubercle was, all along, the secret cause which only declared itself terminally.

It would seem wisest to account sarcoid a syndrome—a malady, that is, which may perhaps be set in motion by any one of a host of factors, acting singly, in concert, or in sequence, rather than to hold it a disease in the old strict sense of a morbid process having a unitary and unvarying

cause. There is already apparent some tendency to adopt such an attitude, and even to look upon it as yet one more example of failure of bodily adaptation to stress (Selye, 1951).

As to its treatment, recent reports of initial success with cortisone or A.C.T.H. (Siltzbach *et al.*, 1951 ; Lovelock and Stone, 1951 ; Small, 1951) are encouraging, but it is too early yet to assess their real value. No remedy used in the past has proved of an unequivocal value.

Summary

Neurological complications in sarcoidosis are occasionally met with, more commonly in the uveoparotid form of the disease than in other variants. Most often they are of the peripheral neuritic type, but disorder of central nervous function also occurs, with symptomatology proper to the region involved. Four clinical case records are presented by way of example. Sarcoid lesions in the nervous system, whether in nerves or cerebrospinal axis, are the same in histological structure as those seen in other tissues, and, like the latter, presumably represent reaction of indigenous mesenchymal elements to whatever may be the cause (or causes) of the syndrome of sarcoidosis.

I wish to express my thanks to Professor P. C. P. Cloake, Professor W. H. Wynn, Dr. Ernest Bulmer, Dr. J. M. Malins, and Mr. J. M. Small for access to their case records and for the opportunity of examining patients under their care.

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Attention has once again been drawn to the relatively high cost of German medical and scientific periodicals (Bonser and Russell, *Nature*, 1952, **170**, 446). As long ago as 1928 Dr. W. Bonser remarked on the exorbitant cost of German periodicals, and his efforts achieved a reduction of some 20% by 1933. While there is a slight rise in the cost of British and American journals since 1933, due to increased cost of production, the ratio of increase of German periodicals compared with British is over 4 : 1. Before the war complaints were not only of the excessive cost but also of the impossibility of computing the annual cost, owing to irregularity in the number of volumes per year. This same state of affairs exists to-day. "We are sure that it will be agreed that their (German scientists') output is as essential to research as that of other countries, and curtailment of its circulation owing to prohibitive costs is to be deplored."

A NEW DIABETIC CHART

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Practically every physician having charge of diabetics uses a different form of chart for recording the results of tests and treatment given during the course of standardization in hospital. The amount of detail given on the chart, and the guidance given to those using it, will depend not only on the ideas of the physician in charge but also on the circumstances in which it is used. Our problem is the treatment of a large number of diabetics, many of whom are scattered in numerous non-medical wards throughout a large general hospital. In these wards the nursing staff, and in many cases the medical staff, have had little experience in the practical management of diabetes, and it is left to us to supervise the treatment. Partly to meet this difficulty, but also for use in the numerous medical wards, we have devised a new chart, which we feel is worth publishing as it embodies several principles, as well as details, which we have not previously seen. Our aim has been to make it an easy chart to fill in and to read, and at the same time to allow flexibility so that it may be easily adapted to meet the varying requirements of different patients, different stages of standardization, different meal-times, and out-patient use.

Diet Panel

For most of our cases we use a simple unweighed diet, as devised by R. D. Lawrence (1950). This allows an average intake of protein and fat (except in obese cases), and detailed restriction is of carbohydrate only. The carbohydrate is allowed in "portions," each containing approximately 10 g. The number of portions allowed at each meal is recorded in the first column of the diet panel, and if the diet is altered during the period covered by the chart the revised allotment is recorded in the second column, the date of change being written at the top of the column. The revised allotment is, of course, put in the first column of the succeeding chart.

The size and isolation of the panel make it stand out clearly, so that doctors, nursing staff, and patients can see at a glance the carbohydrate allowance at each meal and the time at which it is taken.

Times of Urine Specimens

The most important innovation on the chart is that it draws the attention of all concerned to the importance of *the time over which any specimen of urine is actually secreted*. Blank spaces are provided for recording not only the time at which specimens are passed but also *the time at which the bladder was previously emptied*. We have found this a much more satisfactory method than having fixed times printed on the chart, as the physician may then choose the time of routine urine tests to fit in with whatever meal-times occur in the different wards. He may also arrange to observe either "short-period" or "long-period" specimens, depending on the type of case with which he is dealing. As a routine we arrange for short-period specimens to be tested before the main meals of the day, the bladder being completely emptied half an hour before the

Name .....

DIET

Time	Meal	CARBOHYDRATE 10-gramme portions	
		At start of present Chart	Altered on Date :
	Breakfast		
	Mid-morn.		
	Dinner		
	Tea		
	Supper		
	Bedtime		
TOTAL			

WEIGHT

Date	St.	Lb.

Date								
Time urine passed								
Time bladder previously emptied								
Benedict's Test	Red (or brown) 2%							
	Orange 1½%							
	Yellow 1%							
	Green (cloudy) 0.5%							
	Blue (or clear green) 0%							
Nitroprusside test								
Ferric chloride test								
Insulin	Time							
	Dose							
	Type							
24-hourly spec. of urine	Total glucose excreted in 24 hrs.							
	Acetone Bodies							
	Albumin							
Blood Sugar	Time							
	Mg./100 ml.							
Urine Sugar (Benedict's) (Bladder emptied half an hour previously)								
Other Data (e.g., Hypoglycaemic Attacks, with time, etc.)								

Continued for Seven Days.

specimen is collected. The time of the preliminary emptying is recorded on the chart, its importance thereby being clearly emphasized to the nursing staff and patient, and the period over which the specimen has been secreted being immediately obvious to the observer. Occasionally there is difficulty in obtaining specimens half an hour after emptying the bladder, especially with women, and in these cases the time is increased to an hour or even longer, and the patient's fluid intake increased at the appropriate time. It is then most unusual for further difficulty to be experienced.

With these tests the aim in standardization may safely be to increase the insulin dosage until at least some of these specimens are free of sugar. We feel it is often not sufficiently emphasized to staff and patients that most diabetics satisfactorily standardized on insulin will pass sugar in the urine after a meal, and therefore no attempt should be made to render a long-period specimen sugar-free, or hypoglycaemia is likely to occur. If a chart does not clearly show the period over which any particular specimen is secreted there is bound to be confusion over the significance of results and the action to be taken.

The chart provides space for six tests a day for seven days, but we commonly only use four, leaving two blank. When used by out-patients, testing only two specimens a day, the daily date section is divided into three days, and the chart will last for three weeks.

Recordings on Chart

Results of Urine Tests.—The results of Benedict's test for sugar are recorded in graph form like a temperaure chart, a dot being placed in the middle of the appropriate square, depending on the colour of the reaction. We feel this is a much neater, more objective, and clearer method than the more usual +, ++, +++ scheme, which, however, we retain for the nitroprusside and ferric chloride tests.

Insulin Dosage.—Space is provided for recording the time, dose, and type of insulin (as S.I., P.Z.I., and G.I.) in two large squares for morning and evening. Each of these squares is subdivided into three, so that four-hourly injections may be easily recorded in the treatment of severe ketosis.

Twenty-four-hour Specimens.—We have found the estimation of the total amount of glucose excreted in 24 hours a useful index to the response of cases to diet alone. When a case is admitted which is regarded as suitable for treatment on diet alone, all urine passed in the first 24 hours is collected in a Winchester bottle prepared with fluoride or thymol as a preservative. The laboratory tests the specimen for albumin and acetone, and estimates the total glucose in grammes excreted in the 24 hours. This procedure is repeated about twice a week, and treatment by diet alone continued so long as the figure is decreasing. Marked decreases can occur in the actual quantity of glucose excreted in the 24 hours before there is any change in the routine daily qualitative tests, and we think the more frequent use of this simple procedure may help to avoid the unnecessary use of insulin in a number of diabetics.

Blood Sugar.—Space is provided for recording the time the blood was taken, the blood-sugar result, and a simultaneous short-period urine test for sugar. These are grouped together because consideration of the results gives some indication of the renal threshold. When the urine is sugar-free it is obvious that the blood-sugar figure is below the renal threshold. But when sugar is present there are two possibilities. Either the blood-sugar figure is above the threshold or the blood sugar *was* above the threshold at the beginning of the period of secretion of the urine specimen but has been falling quickly and is below by the time the estimation is made. If, therefore, sugar is present in the simultaneous urine specimen a further urine test is necessary before an assessment of the renal threshold can be made. This second specimen should be passed as soon as possible after the first, usually 20 to 30 minutes, and, of course, no food should be taken during this time. Sugar in the second specimen shows that the blood-sugar figure is above the threshold; if sugar is absent the figure is below. This method probably gives as accurate an assessment of the renal threshold in relation to a single blood sugar as possible, but it should be remembered that if the bladder is not completely emptied each time urine is passed the results will be false.

Other Data.—Space is provided at the bottom of the chart for recording any other details, such as hypoglycaemic attacks, intravenous therapy, blood pressures, blood urea, and other investigation results.

Notes on the Back.—We have found it helpful to print notes on the back of the chart giving guidance in its use, and also giving details of Benedict's test, the nitroprusside test, and the ferric chloride test. There are also included details of a regime to be employed for severe ketosis, when soluble insulin is advisable every four hours but the patients are able to take feeds by mouth. Such treatment, once instituted by the doctor, can then be continued by the nursing staff.

Comments

At first sight the chart may appear somewhat complex, but in practice the members of our nursing staff have received it with enthusiasm, and have found it extremely simple to use. We feel that any sister who is not prepared to keep it accurately is unsuitable to nurse diabetics. It has also been found very helpful in instructing the junior staff.

The chart is a large one, but we have found this no disadvantage, as special boards have been made on which to mount it. Before we had the special boards quite satisfactory results were obtained by mounting it on a piece of cardboard with paper clips. In actual practice, its size makes it easier to fill in and clearer to read.

Summary

A new form of diabetic chart for use in hospital standardization is described and illustrated.

Stress is laid on the importance of recording on the chart the time over which specimens of urine are secreted. This is achieved by providing space for the time the bladder was previously emptied as well as the time the urine specimen was passed.

Attention is drawn to the fact that most diabetics satisfactorily standardized on insulin will have glycosuria immediately after a meal, and therefore, as a routine, short-period specimens before meals are the most helpful.

A simple method is described for determining the relation of the renal threshold to a single blood-sugar result.

We would like to thank the Central Wirral Hospital Management Committee for its willing co-operation in the production of this chart.

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Seventy-eight Japanese patients with radiation cataracts caused by the atomic bomb dropped on Hiroshima have been re-examined, five years after the explosion, by the medical department of the Atomic Bomb Casualty Commission clinic in Hiroshima (*Science*, 1952, **116**, 322). This group of patients was almost entirely drawn from the 922 survivors who were at less than 1,000 metres (1,094 yd.) from the hypocentre of the explosion: among these there was an incidence of cataract of 9.8%. On the day of the explosion at least half of the 78 patients re-examined had experienced fever, purpura, epilation, amenorrhoea, and vomiting, which suggested that they had received severe irradiation. The fact that all except one of the 78 patients suffered from scalp epilation is noted. Although the "shielding factor" was not studied specially, it is recorded that there were no cataracts in survivors who were in a large concrete building 800 metres from the hypocentre of the explosion. When this follow-up study was made there was no evidence of blood dyscrasias in the patients with radiation cataracts; in fact, radiation cataract was the only finding attributed to the late effects of the atomic bomb.

Medical Memoranda

Chronic Arsenical Poisoning Due to Prolonged Administration of a Bromide and Arsenic Mixture

As a result of the introduction of numerous new drugs and of the vast increase in consumption of medicines by the general public, cases of drug intoxication have become extremely common. The use of bromides has diminished a great deal, partly because of the increasing use of barbiturates, but even when a bromide mixture was the stock sedative chronic arsenical poisoning as a result must have been very rare. The following case is therefore worth recording.

Case Report

A woman aged 59 was admitted to hospital on April 12, 1951, complaining of various symptoms since October, 1950, including palpitations, tiredness, nausea, and vomiting of watery fluid. By December her weight had fallen from 9 st. to 7 st. 2 lb. (57.2 to 45.4 kg.), and at that time she noticed brown pigmentation of the skin of the back. In February, 1951, she had palpitations, nausea, and flatulence, but no vomiting; lassitude was severe, and the pigmentation of the trunk was more pronounced. The patient had had pneumonia at 13 years, a hysterectomy at 31, and paralysis of the legs with severe pains in the back at 35—no further details of the latter could be obtained, but the history suggested an attack of sciatica. She smoked up to 30 cigarettes daily and took little alcohol.

On clinical examination she was seen to be a thin, active, talkative woman. She had generalized brown pigmentation of the skin, particularly well marked over the lumbar region and over the upper part of the abdomen. There was no pigmentation within the mouth. Very little axillary hair remained, but in other situations the hair was normal. The heart was normal and the blood pressure 190/90. The lungs and abdomen were normal. The nervous system was normal, except that the tendon reflexes were slightly diminished; there was no sensory disturbance.

Various investigations were carried out: the urine was normal chemically and microscopically; blood count normal; glucose-tolerance test normal; blood Wassermann reaction negative; chest *x*-ray film normal.

As the commoner causes of pigmentation of this type had by now been excluded, the possibility of chronic arsenical poisoning was considered. On close questioning the patient confessed that about 18 years before a mixture had been prescribed for her "nerves"; she had found this very satisfactory and had continued to take it regularly each night without further reference to her doctor. The prescription proved to be as follows: sodium bromide, 10 gr. (0.65 g.); chloral hydrate, 5 gr. (0.32 g.); liquor arsenicalis, 2½ minims (0.15 ml.); extractum glycorrhizae liquidum, 5 minims (0.3 ml.); aqua chloroformi ad ½ oz. (1 ml.). A specimen of the patient's hair was forwarded to the Liverpool City analyst, who reported that the arsenic content was much increased, and contained arsenic equivalent to eight parts of arsenic trioxide per million.

The bromide mixture was discontinued and there was an immediate improvement in her condition. When she reported at the out-patient clinic on June 27, 1951, she was free from palpitations and was sleeping well. The pigmentation was much less marked. Her weight had increased from 7 st. 2 lb. (dressed) to 7 st. 9¾ lb. (undressed) (45.4 to 48.9 kg.).

Comment

It is of interest that this woman continued to take the mixture regularly each night for many years without any further reference to her doctor. She would thus take about 1/38 gr. (1.7 mg.) of arsenic trioxide daily for a period of over 17 years before toxic effects were produced. Clinically many of the characteristic features of chronic arsenical poisoning were absent—there was no neuritis, no pharyngitis

or laryngitis, no conjunctivitis, and no hyperkeratosis; the diagnosis was made on the history, the pigmentation, the increased arsenic content of the hair, and the rapid improvement when the mixture was discontinued. This case serves to emphasize the necessity for considering drug intoxication when any unusual syndrome is encountered.

I wish to thank Dr. Mary T. Penrice for various clinical details and for the prescription of the bromide mixture; I would also like to thank Dr. J. F. Clark for his estimation of the arsenic content of the hair.

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Perforations of the Small Intestine by Ingested Non-metallic Foreign Bodies

Intestinal perforation by ingested non-metallic foreign bodies is an uncommon occurrence, and the largest personal series recorded is that of Ginzburg and Beller (1927) who reported 12 cases which occurred at the Mount Sinai Hospital in the preceding decade.

The following conclusions may be drawn from their paper: (1) Impaction of the foreign body usually occurs at the caecum or flexures of the colon. It is unusual for the small bowel to be involved unless a large hernia or Meckel's diverticulum is present. (2) The foreign body impacts transversely and usually produces one area of necrosis in the bowel wall through which it perforates. Sometimes it impacts as above, but produces two areas of necrosis and two perforations. More rarely still the impacted foreign body frees itself and passes on, but perforation occurs later from sloughing of the involved bowel wall. (3) The perforation produces either acute or chronic symptoms: the latter is more often the case, and results in a localized abscess or an inflammatory tumour. Cases resulting in acute peritonitis are very infrequent.

Three cases of acute peritonitis due to perforation of the small bowel by non-metallic foreign bodies are recorded, all of which occurred during September, 1948. In each case a provisional diagnosis of acute appendicitis was made.

Case 1

A farmer aged 52 was admitted to hospital complaining of diffuse lower abdominal pain of 20 hours' duration which had gradually become worse. He had vomited six hours after the onset of the pain and on several further occasions before admission. On examination his temperature was 99° F. (37.2° C.), pulse 96, and respirations 18. The whole lower abdomen was rigid and tender, tenderness being most marked in the lower right quadrant, and the pelvic peritoneum was tender to rectal examination.

Operation.—The approach was through a muscle-splitting incision in the right iliac fossa. The peritoneum was inflamed and there was a fair amount of free blood-stained serous fluid in the peritoneal cavity. The appendix was normal, but on examining the lower ileum a mass was felt which proved to be a large Meckel's diverticulum perforated at its fundus by a thorn 1¼ in. (3.8 cm.) long, and with surrounding loops of small bowel attached to it by fibrinous adhesions. The Meckel's diverticulum was excised and appendicectomy performed. Recovery was uneventful.

Case 2

A man aged 41 was admitted to hospital complaining of lower abdominal pain of 12 hours' duration. He had eaten fish for supper the previous evening, and was awakened early on the morning of admission by the pain, which later improved somewhat so that he went to work; but it became more severe towards midday, and he had to return home. On examination his temperature was 97.8° F. (36.6° C.), pulse 76, and respirations 20. There was marked tenderness and rigidity in the right iliac region of the abdomen, but rectal examination revealed no abnormality.

Operation.—The approach was through a muscle-splitting incision in the right iliac fossa. The peritoneal cavity contained an excess of serous fluid, the appendix was normal, but about 18 in. (45.7 cm.) from the ileo-caecal junction a fish bone 1¼ in. (3.8 cm.) long was impacted transversely across the ileum, perforating the bowel wall on each side: there was considerable inflammatory reaction but no gangrene of the bowel at the sites of perforation. The bone was removed, the perforations were sutured, and appendicectomy was performed. Recovery was uneventful.

Case 3

A man aged 48 was admitted to hospital with a complaint of intermittent abdominal pain of three days' duration, starting 15 hours after a meal of roast chicken. At first the pain was diffuse and most marked just below the umbilicus; but some minutes after its onset the pain suddenly intensified and the patient vomited twice. Since then intermittent attacks of similar pain but of milder intensity occurred until the morning of admission, when it became constant and more severe. On examination the temperature was 99.8° F. (37.7° C.), pulse 100, and respirations 20. The tongue was coated and the breath foul; there was generalized abdominal rigidity and tenderness, principally in the umbilical region; the pelvic peritoneum was tender on rectal examination, and peristaltic sounds could be heard.

Operation.—The approach was through a right paramedian incision. The peritoneal cavity contained a quantity of turbid fluid, and a loop of the upper jejunum was found with two perforations, one on each side of the bowel, sealed off by adherent omentum: there was commencing gangrene of the bowel wall at the sites of perforation. A search was made for the foreign body, and a piece of chicken bone 2 in. (5 cm.) long was felt in the caecum and removed. The damaged loop of jejunum was excised and an end-to-end anastomosis performed. The patient made an uninterrupted recovery.

Discussion

Foreign Body.—Fish bones and chicken bones are usually found in perforations of this type: a thorn, like other vegetable matter, is an uncommon finding (Macmanus, 1941; Macfarlane, 1948).

Site of Impaction.—A Meckel's diverticulum is recognized as a likely site for impaction of any intestinal foreign body, and transverse impaction in the lower ileum, although far from common, is the usual site for a perforation causing acute peritonitis (Ginzburg and Beller, 1927). Impaction with perforation of the jejunum, however, as in Case 3, is most unusual, and occurred only twice in the 95 cases of intestinal perforation due to ingested foreign bodies of all types collected and reviewed by Macmanus (1941).

Mechanism of Perforation.—In Case 3 the bone was impacted transversely, caused two areas of necrosis which subsequently perforated, and then freed itself. This unusual mechanism was probably due to the relatively large diameter of the small intestine in the upper jejunum.

Type of Pain.—In Cases 1 and 2 the pain would appear to have been due to the peritonitis, but in Case 3 the man suffered intermittent attacks of central abdominal pain over a period of three days before it became constant. It seems justifiable to assume that during this period the pain was caused, not by peritonitis, but by spasm of the bowel, possibly due to a local reflex.

Peritonitis.—The infection was of a low grade in all the cases on account of minimal peritoneal soiling. This was due partly to blockage of the perforation by the foreign body and partly to the peritoneal reaction, which had good time to develop in each case.

I am indebted to Mr. J. O. D. Wade, surgeon to the United Cardiff Hospitals, for his advice and criticism in presenting these cases.

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Reviews

RESPONSE TO INJURY

The Metabolic Response to Surgery. By Francis D. Moore, M.D., and Margaret R. Ball, A.B. Metabolic Diagrams by Mildred B. Codding, A.B., M.A. (Pp. 156; illustrated. £2 15s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952.

The professor of surgery at Harvard and his colleague have produced a unique and original book; it may well herald a change in the approach to the patient after operation. The complex graph on the dust-cover, showing in tabular form a patient's metabolic behaviour after operation, clearly reflects the modernity and the novelty of the content in its superimposed graphs, whose hatched-in and shaded masses above and below each baseline suggest a cubist representation of giant skyscrapers on a waterfront, reflected in the water below them. This type of graph is indeed symbolic of the authors' approach to the problem—graphs of the temperature and pulse rate, nitrogen, potassium, sodium, and calcium balance, eosinophil count, and therapy being indicated in parallel blocks. The complaint is sometimes made that such tables are too complex and difficult to follow, but it must be admitted that the metabolic behaviour of a patient after operation is no less complex and difficult to follow. Dr. Moore's essay analyses and integrates these changes.

The average clinician may be confused no less by the complexity of the diagrams than by the expression of electrolyte concentrations in milli-equivalents, but there is nothing more certain than that the milli-equivalent will in this sphere replace the milligramme soon, and no conception of the balance of a patient's electrolytes can be obtained unless the milli-equivalent is used.

Dr. Moore's thesis, which he goes far towards proving, is that during the first few days after operation or injury the metabolism undergoes a natural biochemical reaction which is normally beneficial and which probably should not be subjected to interference provided it proceeds normally. This normal metabolic response is characterized, according to Dr. Moore, by a transient slight rise of temperature and pulse rate, a transient decrease in urinary excretion, a loss of nitrogen from the body for three to seven days followed by a positive nitrogen balance, a loss of potassium for two to five days followed by potassium retention, a decreased urinary excretion of sodium for two to five days followed later by sodium diuresis, a loss of weight greater than can be accounted for by these balance changes and due to oxidation of fat, a variable drop in circulating eosinophils and an increased excretion of steroid hormone products under endocrine influence, and a period of starvation and relative caloric deficiency.

If these changes are a beneficial reaction, we must accept Dr. Moore's advice not to treat the fever with antibiotics, not to swamp the patient with water during the early post-traumatic phase to make up urine volume to an arbitrary level, not to try to cover up short-term nitrogen loss by unsuitable protein material, not to be anxious about potassium for three days after operation, not to make the patient oedematous by the administration of sodium during the phase of sodium retention, not to be concerned with caloric deficiency for the first three days, not to prolong the starvation phase beyond three to five days, and not to convert a normal convalescence into a "failed" convalescence by meddlesome early interference.

Dr. Moore does, however, recognize four abnormal types of response of which particular account must be taken: (1) the excessive response to excessive trauma; (2) the depletion response of a patient depleted before operation; (3) the hypo-adrenal response (which is less clearly proved than the others); and (4) the extrarenal loss response in a patient who, in the early post-operative phases, loses water, electrolytes, and protein by abnormal routes.

The book is a brilliant analysis of an immense quantity of data. British clinicians working in the same field will have the greatest possible admiration for it, tempered a little by their appreciation of Dr. Moore's enthusiasm for the almighty adrenal cortex. It is a book which anatomizes clearly and in detail the methods by which the problem of the post-operative patient can most profitably be attacked, and there is no question that its study will help surgeons to a greater understanding of the physiology of the whole patient and to greater surgical success.

IAN AIRD.

TEXTBOOK OF PHARMACOLOGY

A Textbook of Pharmacology: Principles and Application of Pharmacology to the Practice of Medicine. By William T. Salter, M.D. (Pp. 1,240; 284 figures. £3 15s.) London: W. B. Saunders Company. 1952.

The author of this book is one who, to quote his own words, "has spent many hours at the bedside of clinical patients as well as long nights in the laboratory." His presentation of pharmacology should therefore appeal to those whose approach to the subject is clinical. The book is divided into four parts: the first is on general principles, the second on the action of drugs on physiological mechanisms, the third on the application of drugs in clinical medicine, and the fourth on toxicology.

The discussion of the principles follows a conventional pattern and is limited to history, pharmacy, and the administration and action of drugs. Although the author acknowledges the importance of the kind of pharmacology that lies nearer to the exact sciences than to therapeutics, he passes lightly over fundamental notions. In a book of this size he might well have devoted more space to the principles of biological assay, the combined actions of drugs, methods of studying the fate of drugs in the body, and the design of clinical trials. But in the second and third parts the author's gift of exposition is fully displayed. To the description of the actions and uses of drugs he brings a formidable array of data drawn from many sources, as the extensive bibliography at the end of each chapter testifies. The discussion of each type of drug follows an orderly and comprehensive arrangement under the headings of history, source, chemistry, actions and fate, clinical application, preparations and doses, standardization, unsolved problems, and synopsis. In Part 3 the author places more emphasis on therapeutics and discusses chemotherapy, actions of drugs in various diseases, gases and vapours, metabolic pigments, and poisons.

The text is in double columns and the print clear; the illustrations, graphs, and tables are excellent. The style is pleasantly discursive. This book is useful because it looks both ways; not only does it help to explain pharmacology to the clinician, but it conveys to the laboratory worker a clear picture of how drugs may be used for their effects on man.

HENRY ADAM.

ART OF MARRIAGE

The Art of Marriage. By Mary Macaulay, M.B., Ch.B. (Pp. 97. 7s. 6d.) London: Delisle. 1952.

Popular books on sex require to be written with the greatest discretion if they are not to err either on the side of sentimentality (usually combined with inaccuracy) or on that of potential pornography. Dr. Mary Macaulay has managed to steer clear of both extremes and has produced a book which is human, scientifically accurate, and fully in conformity with current sexual ethics. It should bring enlightenment and comfort to innumerable married couples or those intending to marry.

The standard of marriage envisaged is that of Christian marriage as understood by most Churches other than the

Roman Catholic. This means that Dr. Macaulay regards marriage as a permanent relationship possessed of spiritual significance as well as social validity. The only exception that the Roman Catholic reader could take to the book is the author's advocacy of artificial contraceptive methods.

Although we are well aware of the heavy costs of book production obtaining nowadays, we cannot but help feel that 7s. 6d. is a high price to have to pay for such a short book so indifferently produced (our review copy, for example, was bound up all wrongly).

E. B. Strauss.

ANAESTHESIA

Principles and Practice of Anesthesiology. By Vincent J. Collins, M.D. (Pp. 528; 99 illustrations. £3 15s.) London: Henry Kimpton. 1952.

Twenty years ago the resident anaesthetist learnt his subject from a chapter squeezed into a textbook of surgery; but now the specialty of anaesthesia has divided internally into several subsidiary ones, and it is doubtful if a single author can describe them all adequately and authoritatively. This is the predominant fault of Dr. Collins's book. He sets out to describe the physics, physiology, and practice of analgesia and anaesthesia, and none of the three is given the comprehensive account it deserves. His description of the signs and administration of general anaesthesia is sound, but thoracic anaesthesia, physics, physiology, spinal analgesia, and various local techniques have already earned separate monographs.

British readers will notice several shortcomings: the doses of curare and neostigmine advised are far too low, and no mention at all is made of xylocaine, trichlorethylene, or the methonium compounds. The section on spinal analgesia contains much outdated advice, and dangerously lacks emphasis on the importance of oxygen with high spinal analgesia. Dr. Collins writes of the "mythical" negative pressure in the epidural space, but this is real enough and can be measured. The section on dental anaesthesia is too brief, and contains the odd statement that music chosen by the patient allows nitrous-oxide anaesthesia to be established and maintained with 25% oxygen.

Gordon Ostlere.

PATHOLOGY OF THE EYE

Clinical Pathology of the Eye: A Practical Treatise of Histopathology. By Bernard Samuels, M.D., and Adalbert Fuchs, M.D. (Pp. 420; 418 illustrations, 191 in full colour. £7 7s.) London: Cassell and Co. 1952.

Ophthalmology is probably the most exact of all clinical subjects, but its pathological basis is distinctly slender. Patients do not die of eye disease, and the removal of an eye at an ordinary post-mortem examination presents difficulties of its own, so that histological studies are largely limited to such affections as lead to the loss of an eye. The histology of severe inflammations, injuries, and tumours of the eye has been well worked out, but for most eye diseases the material is scanty. It is mainly for this reason that no adequate textbook on ocular pathology is available. There are many excellent treatises emphasizing one or other aspect, frequently to the exclusion of important material in other fields, but a comprehensive review has still to come.

This book is the work of two clinicians who have contributed extensively to ocular pathology. Dr. Fuchs's *Atlas of the Histopathology of the Eye* has been of great help to many generations of students, and the appearance of many of his illustrations in the present volume is welcome. Their technical excellence now enriches a text as sumptuously produced as the illustrations themselves. The chapters on those aspects of pathology which are well established are adequate. A gratifying innovation is the chapter on post-operative pathological findings, even if inevitably there is more information on surgical complications than on the normal process of healing. The suggestion that eye banks should pass on to pathologists successfully operated eyes that have come to excision is a *cri du cœur* on the scantiness of material in other fields no less than in surgery. The chapter on the retina approaches most closely the scope the authors have put on their work: ophthalmoscopic findings rather than specific conditions are interpreted in terms of histological changes. On the whole the text, even if unnecessarily vague on some aspects and rather dogmatic on others, represents orthodox teaching on the histopathology of the eye.

Arnold Sorsby.

CEREBRAL ANGIOGRAPHY

The Normal Cerebral Angiogram. By Arthur Ecker, M.D., Ph.D. (Pp. 190; 139 illustrations. 47s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1952.

The first one-third of this book is given over to a detailed account of the author's technique, including percutaneous puncture of the carotid and vertebral arteries, and the *x*-ray projections which he favours. One suspects that many more films are taken than is the usual practice in Britain. A chapter is given to the complications of angiography, an aspect of the subject which tends to be ignored in many books. The author pays particular attention to the dangers of respiratory embarrassment, leading to cerebral anoxia, during and after angiography. This can be a serious complication, particularly in patients drowsy from premedication or from the nature of the intracranial lesion, and one which attracts too little attention. The author takes the special precaution of providing the patient with the undivided attention of a nurse for an hour after the procedure.

The rest of the book is devoted to a description of the normal anatomy of the intracranial blood vessels, profusely illustrated by angiograms. For the most part the reproductions are clear, but some might well have been omitted, because the vessels cannot be clearly discerned. To one (Fig. 82) the incorrect caption has been applied. It is unfortunate and somewhat irritating that, where the anatomy of a vessel is being described, references are not given in the text to suitable illustrations, although an index of vessels is provided.

Although this book sets out to describe normal angiograms, the temptation is too great to avoid including some abnormal ones. This for the reviewer indicates the doubtful value of a book devoted to the normal; its value would have been much enhanced if normal and abnormal positions of vessels could have been contrasted, in order to emphasize the relative importance of individual vessels. A large experience of normal angiograms is necessary in order to interpret correctly the supposed abnormal, and in a study of the normal there is a risk of placing too much emphasis on the smaller vessels and of forgetting the wide variations in position to which they are subject. For this reason caution must be used in the diagnosis of tentorial and cerebellar herniation by angiography. The author provides an interesting and stimulating chapter on the relations of blood vessels at the tentorial hiatus and at the foramen magnum. But it is questionable whether any one of the vessels at these levels runs a course sufficiently constant to constitute a norm from which displacements might be measured. Nevertheless, it is proper that attention be drawn to vessels which may be displaced by internal herniations, for such study may help to illuminate the mechanism by which these herniations bring about changes in the clinical picture. The author's statement that "it has become our practice to perform cerebral angiography in brain tumour suspects before performing lumbar puncture or pneumoventriculography" implies great confidence in the ability to diagnose internal herniation by angiography. In the present state of experience this seems a dangerous doctrine; the diagnosis of herniation can be more safely based on sound clinical judgment. Although well produced, the price in this country is wellnigh prohibitive for a book of 190 pages.

D. W. C. Northfield.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 25 1952

THE ACUTE RADIATION SYNDROME

The acute radiation syndrome is the name that has been given to the signs and symptoms caused by exposure of the whole or a large part of the body to ionizing radiation. It is an acute illness lasting a few weeks and differs from chronic radiation injury caused by repeated small doses of radiation. Much of the knowledge about this syndrome has been derived from the information gained at Hiroshima and Nagasaki, but this has been supplemented by more accurate and detailed records of the few cases which have occurred among workers in nuclear energy research. Hemplemann, Lisco, and Hoffman[1] have published an account of what happened to 10 persons injured in an accident several years ago at the Los Alamos scientific laboratory. These cases are unique and the detailed report on the clinical, haematological, and pathological aspects of the illness that developed is of great interest.

Of the 10 persons exposed to bursts of penetrating ionizing radiation two died. One of the survivors showed the signs of the acute radiation syndrome, and haematological changes were found in four others. There was no effect of heat or blast in these accidents, the patients being exposed to fast neutrons and hard gamma rays. The bulk of the tissue damage was done by the neutrons, which were absorbed in the superficial layers of the skin and subcutaneous tissues. The patients were not irradiated uniformly throughout, and the superficial injury was mainly of the hands and the abdomen.

The two fatally injured patients had a prompt initial reaction characteristic of the acute radiation syndrome, with nausea, vomiting, prostration, and a mild fall in blood pressure. They recovered from this during the first or second day and then remained fairly well for about one week, when they developed fever, loss of weight, and gastro-intestinal symptoms. They were given whole blood, plasma, fluids, and penicillin, but death occurred in one patient on the ninth day and in the other on the twenty-fourth day after the accident. The more heavily irradiated patient had paralytic ileus of such severity that it required continuous gastric suction. This patient became jaundiced, with mild haemorrhagic manifestations, and developed circulatory collapse just before death. The other patient had a more gradually developing fever, mild diarrhoea, abdominal distension, severe stomatitis, and died without any signs of haemorrhage. In addition to the general reactions these patients suffered very severe damage to the tissues of their heavily irradiated upper extremities and some damage to the skin over their trunks. The reaction on the arms in both cases was almost immediate, owing to the overwhelming nature of the dose delivered—equivalent to tens of thousands of roentgens. Subcutaneous oedema and changes in the peripheral blood flow were noted within a matter of minutes. Blisters formed within three days, and the patient who lived for 24 days lost the whole of the skin of the hands and both forearms, with some underlying late ischaemic necrosis. This patient also had moist desquamation of the skin of the abdomen, and loss of hair of the scalp and beard.

Only one of the survivors showed signs of the acute radiation syndrome. He had an initial reaction of nausea and vomiting of moderate degree. During the next two weeks he had a short bout of fever and prostration of several days' duration, and during the third week he lost some of the hair of his scalp and beard. For several months he was severely exhausted by any slight effort. There was evidence of severe damage to the germinal tissues, which was, however, temporary, but some years after exposure this man, although in good health, developed bilateral radiation cataract; the first, in the left eye, came on three years after exposure. The six other survivors had no symptoms of any kind and are in good health three and a half years after the accident.

The exact dose of radiation received by each of the people exposed is not known. In addition to the penetrating radiations there was an unknown but large amount of beta rays and very soft secondary *x* rays. The radiation received was not evenly distributed, but an estimate was made both of the integral dose and also in terms of the surface radiation dose from gamma rays and soft *x* rays for the whole body. The two patients who died were thought to have received respectively 8.41 and 9.5 megagramme-roentgens: expressed in another way, the first man had a total body dose of 480 roentgens of 80 kV *x* rays and 110 roentgens gamma-ray dose, and the second man 1,930 roentgens of 80 kV *x* rays and 114 gamma-ray roentgens. The patient who survived but had the acute radiation syndrome was estimated to have received 2.72 megagramme-roentgens, or 390 roentgens of 80 kV radiation and 26.4 gamma-ray roentgens. One other patient had just over, and

[1] *Ann. intern. Med.*, 1952, **38**, 279.
[2] *Cancer Res.*, 1952, **12**, 315.

another just under, 1 megagramme-roentgen, each receiving between 100 and 200 roentgens total body irradiation. The other patients had less than half this amount.

Immediate and sustained lymphopenia was noted in most of the exposed people. Neutropenia and thrombocytopenia, of a moderate degree and a temporary nature, occurred only in the more heavily irradiated. An initial, and usually marked, granulocytosis was observed in all of them, and a prompt though temporary monocytosis was noted in six. Five of the six asymptomatic survivors developed eosinophilia. Uncoagulability of the blood was observed in one of the fatally injured patients at the time of death, and several of the survivors showed prolongation of the blood-clotting time. Specific chemical changes in the blood were not found. The necropsies on the patients who died showed widespread destruction in the radio-sensitive organs as well as in the superficial tissues. Death of cells during or shortly after mitosis was very conspicuous in the rapidly dividing tissues. The ductal epithelium of the sweat glands alone among the tissues of the body showed a marked proliferative response. This was thought to be secondary to early damage. An inflammatory reaction was found in many tissues, an unusual feature being an almost complete absence of granulocytes in the cellular exudate.

The conclusions reached from this study were of two kinds. The fundamental nature of the acute radiation syndrome is widespread destruction of tissues throughout the body: this is the basis of the observed physiological and clinical responses. The destructive process differs from the tissue damage caused by other common toxic agents in that they occur primarily in the radiosensitive tissues wherever they may be situated. In this sense the injury is more akin to that caused by certain chemical poisons with a selective action on particular organs rather than to traumatic injuries resulting from heat or crushing. Another outstanding feature is the delay in the appearance of signs of tissue destruction, this delay varying from organ to organ. But in general the overall clinical and constitutional response of a person suffering from the acute radiation syndrome is similar to that observed in other diseases in which tissue death is the prominent feature. The other group of conclusions are related to the treatment. The first is that at present there is no form of treatment which will help the heavily irradiated patient to survive the acute phase of the illness. Tissues may be protected from damage, but there is no known method of saving cells once injury has occurred. But the regenerative powers of most tissues are so great that considerable if not complete recovery will occur if the patient survives the critical toxic stage. Antibiotics, transfusions, and maintenance of the fluid and electrolyte balance are therefore suggested as being helpful.

Work on animals has shown that the number of those surviving after a single large dose of total body irradiation can be increased by measures instituted after the radiation injury has been sustained. These measures include intraperitoneal implants of splenic tissue or injections of embryo suspensions, or intravenous injections of homologous bone-marrow suspensions. The evidence suggests that the substance which helps to overcome the effects of radiation injury under these conditions is likely to be non-cellular and capable of instituting recovery of certain tissues of the body vital to the survival of the animal. Similar results can be attained by shielding certain parts of the animal, notably the spleen, during the exposure to radiation. Jacobson[2] has reviewed the evidence for the existence of a humoral factor concerned in recovery from radiation injury, and further work may provide some opportunity for developing methods of treating those suffering from the acute radiation syndrome who have not received an overwhelming integral dose.

FILARIASIS

Interest in filariasis is increasing rapidly, and the paper by Drs. Ian A. McGregor, Frank Hawking, and Dean A. Smith published elsewhere in this issue describes important work on the subject being carried out in West Africa. In East Africa, too, valuable research is proceeding,[1] and further investigations on a periodic filariasis in the Pacific have been recently reported,[2 3] while in Nigeria Gordon and his team[4] are studying loiasis. At home much basic research has been undertaken by F. Hawking, of the Medical Research Council, and clinical studies have been carried out at the Hospital for Tropical Diseases, London. Considerable interest has also recently been shown in the investigation into filarial "river blindness" in West Africa. This has been sponsored by the British Empire Society for the Blind and is to be directed by Dr. F. Rodger and Mr. G. Crisp.

There are several reasons why filariasis is attracting more attention. Filarial infections have always been dreaded because of the deformities they may produce, and military activities in the Pacific during the last war emphasized their importance. Rightly or wrongly, 10,000 out of a total of 38,000 men of the American Naval Force serving in that theatre were repatriated with early filarial infections. No efficient

antifilarial drug was then known, and this experience led to a large-scale search for one. As a result, diethylcarbamazine ("hetrazan," "banocide") was discovered.[5] Therapeutic trials with the drug have been carried out in many countries, and the introduction of this new remedy has encouraged fresh study of the disease. Interest has also been increased by work done in the Medical Research Council's Nutrition Research Unit in the Gambia. There attention has been drawn to the part filarial infections may play in aggravating malnutrition by competing for nutrients with the human host.

The most important filarial infections in man are those caused by *Onchocerca volvulus, Wuchereria bancrofti, Loa loa,* and *Acanthocheilonema perstans.* No clinical results of infection with the last named are known, though the effect of diethylcarbamazine on the parasite is of interest and has been studied by McGregor and his co-workers. Treatment of onchocerciasis has been less successful than that of other filarial infections. This is especially unfortunate because in advanced cases ocular lesions develop and are responsible for the "river blindness" which the British Empire Society for the Blind team hope to investigate. There have been several surveys of the incidence of this disease, and among the more recent is the exhaustive study of Buckley.[6] He found the incidence of infection in different districts in Kenya to vary from 20% to 72% of the population, and ocular complications to occur in 10% to 15% of those affected. The latter are so common in the Kodera Valley that it has become known as the "Valley of the Blind." In West Africa, too, similar "Countries of the Blind" are known. In the New World onchocerciasis is found in Mexico and Guatemala. It is known that the *Simulium* flies, which are the vectors of onchocerciasis, breed in rapidly running streams and rivers. Garnham and McMahon[7] prevented the flies from breeding by adding D.D.T. to the headwaters of streams, and they put this method into operation at Koder. Four years later McMahon reported[8] that the incidence of the infection as judged by standard tests had fallen from 37% to 1% among children aged 4–8 years living in the "Valley of the Blind" at Koder. This is a particularly gratifying result because of the comparative ineffectiveness of diethylcarbamazine in treating the disease.

As to *W. bancrofti* infections, Santiago-Stephenson and his colleagues[9] showed that, after treatment with 6 mg. diethylcarbamazine per kg. of body weight daily for 21 days, the great majority of microfilariae disappear from the blood. Evidence of death of adult worms was also found. In East Africa the Filariasis Research Unit has shown that 10 mg. of the drug per kg. body weight daily for seven days is effective and more practicable than longer courses, since Africans often default after a few days' treatment. Fewer side-effects of treatment appear to have occurred in East Africans than in patients in the Gambia. Many patients with asymptomatic *W. bancrofti* infections have been treated as part of the unit's programme, and these are being followed up in an attempt to determine whether treatment prevents the development of complications such as elephantiasis. The unit has confirmed that earlier American reports of the value of diethylcarbamazine in elephantiasis are without foundation. In addition to studying the treatment of filariasis with drugs, this unit is also investigating the effect of filarial disease on the economy of the local inhabitants, and is developing methods of controlling the infection. There have been few studies of the control of filariasis with diethylcarbamazine in the field, and the paper in this issue by Dr. McGregor and his colleagues is of special interest in this respect.

Gordon and his co-workers[4] have done much to clarify knowledge of the epidemiology of loiasis. They have found that the larval forms of the fly vectors of the disease, *Chrysops silacea* and *C. dimidiata,* live in densely shaded, slow-running streams, and the adult female flies normally dwell in the high forest canopy. Houses sited on hills, so that they form breaks in this canopy, are specially liable to be entered by the flies and their inhabitants to become infected. Diethylcarbamazine is highly effective in loiasis, and treatment with it causes the death of the microfilariae and the adult worms. The drug appears to act on microfilariae by so sensitizing them that they are removed from the blood and destroyed by macrophages in the liver. Advances in knowledge relating to loiasis have recently been discussed in detail by Woodruff.[10]

Filariasis affects large numbers of people within the British Commonwealth, and it is therefore especially gratifying that research on it is being so vigorously carried out. The participation in this research of voluntary organizations, such as the British Empire Society for the Blind, is welcome, and it is to be hoped that their example will stimulate the Government to support further work on the many problems awaiting solution.

[1] East Africa High Commission, *Filariasis Research Unit, Annual Report,* 1951.
[2] Manson-Bahr, P., and Muggleton, W. J., *Trans. roy. Soc. trop. Med. Hyg.*, 1952, **46**, 301.
[3] Buckley, J. J. C., ibid., 1952, **46**, 321.
[4] Ibid., 1950, **44**, 11.
[5] See *British Medical Journal*, 1951, **2**, 659.
[6] *J. Helminth.*, 1949, **23**, 1.
[7] *Bull. ent. Res.*, 1947, **37**, 619.
[8] East African High Commission, *Filariasis Research Unit, Annual Report,* 1951, p. 73.
[9] *J. Amer. med. Ass.*, 1947, **135**, 708.
[10] *W. Afr. med. J.*, 1952, n.s. **1**, 45.

MODERN ANALGESICS

Ever since Sertürner first isolated morphine from opium in 1816 the search has continued for the ideal analgesic. Morphine continues to be the most efficacious remedy for severe pain and remains to this day the most widely used analgesic drug. But its undesirable side-effects, including the tendency to cause addiction, have led organic chemists to seek effective substitutes, and elsewhere in this issue Dr. P. W. Nathan describes a clinical study in which some of the newer synthetic drugs have been compared with each other and with morphine.

Such a clinical trial can be effectively carried out only when the subjects experience fairly severe pain. Asher[1] has shown that, if the pain is of mild or moderate severity, some relief can be given to 50% of subjects by inert tablets administered by mouth. Nathan's patients had severe, chronic pain which never disappeared spontaneously, and the results, assessed by the subjective but reliable method of Professor Keele's "pain charts,"[2] go far towards confirming the clinical value of pethidine and amidone. The doctor's traditional ¼ gr. (16 mg.) of morphine is shown to have the same analgesic effect as 125 mg. of pethidine, or 12 mg. of amidone. On occasion, 2.5 mg. of the latter can be an effective dose. Morphine has the great advantage that by increasing the patient's sense of detachment from his environment, and by relieving apprehension, it induces a mild euphoria and drowsiness which in certain circumstances are most desirable. Such an effect can be obtained with the other drugs, except in larger doses, only by the simultaneous use of a barbiturate sedative. The oral and parenteral doses of amidone and pethidine are similar, but the side-effects, which resemble those of morphine, were more common after injection in Nathan's patients. Of the several new drugs tested, no single one was found to be less toxic than the others; intolerance to one drug did not imply that the others could not be taken, and it is therefore useful to have a selection from which to choose for the sensitive patient. In Nathan's experience, addiction to these drugs did not develop in any patient after a successful pain-relieving operation had rendered the further administration of the analgesic unnecessary. His trial has confirmed the general experience that phenadoxone is not a clinically useful analgesic, despite initial reports.[3] Inconsistent results are obtained from oral administration, and the injection of even 20 mg. may be dangerous.

The practitioner is frequently besought by his patients to provide relief for pain, and it is only infrequently that these powerful remedies need be used. Aspirin and phenacetin are effective and useful, and a sedative effect is obtainable if a barbiturate is combined with them. Modern soluble preparations of calcium aspirin are pleasant to take, and the side-effects are minimal. The reputation of codeine as a pharmacologically useful drug is at present waning, for the analgesic effect of the compound tablet of codeine *B.P.* is probably due more to its content of aspirin and phenacetin than to the ½ gr. (8 mg.) of codeine present. It is a weak analgesic even when given in full doses, and, furthermore, its efficacy as a depressant of the cough centre has been recently challenged by Hillis.[4] His results showed that its effects were no greater than could be explained by suggestion, a finding which has surprised many doctors who have prescribed it for years with enthusiasm, faith, and apparently satisfactory results.

[1] *Lancet*, 1948, **2**, 771.
[2] Ibid., 1948, **2**, 6.
[3] Wilson, W. M., and Hunter, R. B., *British Medical Journal*, 1948, **2**, 553.
[4] *Lancet*, 1952, **1**, 1280.

ROTTEN TEETH

The two common dental diseases, caries and pyorrhoea, are diseases of civilization, but, being only rarely the primary cause of death, their prevention lacks the drama attending the prevention of many other diseases. In general, people have grown used to preventive medicine exercising its powers by rapid and simple means, and have for long taken for granted that the public health authorities will protect them from sanitary and environmental hazards without much personal interference. But for a man to change his dietetic way of life is another matter, and only a few seem prepared to undertake this either for themselves or for their children. In accordance with the generally accepted views of the dental profession, a recently published Scottish report[1] attributes the ravages of dental caries mainly to the presence of fermentable carbohydrates in the mouth at most times of the day and night, and it gives excellent advice on a regime of diet to prevent this state of affairs. Assuming, however, that this is a monumental task to accomplish, the report draws attention to the possibilities of fluorine as an agent to inhibit the onset of caries. But whether fluoridation of public water supplies is a sound measure is at present debatable.

The great advances in dental surgery and anaesthesia during this century have made young people to-day accept regular dental treatment as part of their ordinary lives. Consequently they tend to rely on their dentist for the care of their teeth and not upon any efforts of their own. The demand for skilled treatment, particularly for children, has therefore increased in Scotland, as elsewhere, but in that country there are only 1,350 dentists for a population of 5,000,000. Inevitably the local authority dental services for children and for expectant and nursing mothers, in Scotland as in England, are in a bad way. Recruitment is adversely affected by comparison with the possibilities of a career in the other branches of the Health Service. Only one schoolchild in six in Scotland is annually receiving systematic dental care. The Whitley scale agreement has helped to stop the drift from the school dental service, but lack of opportunities still deters men dentists from joining it. A recent circular from the Department of Health[2] cites an encouraging improvement in staffing, though in the absence of figures a proper assessment cannot be made.

The shortage of dentists in Scotland has led the committee that prepared this report to recommend that the school service be augmented by ancillaries such as New Zealand has. It emphasizes that "nothing should

[1] *Preventive Dental Services.* Report by the Subcommittee of the Standing Dental Advisory Committee of the Scottish Health Services Council. H.M.S.O. 1952.
[2] D.H.S. Circular 87/1952.

interfere with the training of dentists or retard the development and enlargement of the dental schools," but ignores the danger that the introduction of women trained to carry out much of the daily work for long carried out by dentists may adversely affect recruitment, not only to the school service but to the dental profession itself. The committee apparently assumes that the New Zealand type of ancillary would also take the place of the oral hygienists at present working in a number of local authority schemes, whose work is becoming appreciated as an important link in the chain of preventive dentistry.

The report covers all the dental services with great thoroughness, including orthodontic treatment. A pilot scheme in Fife, based on a consultant clinic decentralizing the simpler work on to school dentists themselves, has actually been working under the auspices of the committee. The volume of work reported from this pilot scheme may cause controversy, particularly the reference to an average period of five minutes for diagnostic consultations. Orthodontic opinion is unanimous that success in treatment is based on thorough diagnosis, for treatment is usually protracted and expensive. The Fife scheme appears not to have progressed as far as many school orthodontic clinics in England. Many now believe there should be a close association between psychiatry and other branches of medicine when investigating the aetiology of diseases, but this is signally lacking in studies of malocclusion. Crichton-Miller has for long emphasized the relation between teeth and psyche, and there is undoubtedly a field for joint research into the psychology of aggression in relation to teeth. Refreshing indeed is a special reference in the report to the importance of breast-feeding, particularly nowadays when the significance of this time-honoured yet humble process is out of fashion in orthodontic thought.

The committee reveals that an adequate school and priority dental service in Scotland would require a rate ranging between 1d. and 2¾d. in the pound. The ability and resources of local government to develop modern health services have come in for serious consideration since 1948, but, so far as preventive dentistry is concerned, finance would not appear to be a particularly formidable obstacle to progress, in Scotland at any rate.

RESULTS OF VACCINATION

There can be few medical procedures more firmly established and more widely used than vaccination against smallpox, and yet there are still surprising differences of opinion on the correct interpretation of the different types of local reaction after vaccination and revaccination. Mitman[1] has recently presented a clear statement of his views on this question, and these should be helpful to practitioners who have to decide on the significance of the results obtained in their patients as well as to those responsible for framing the form of vaccination certificates. He distinguishes between two types of local reaction: those due to *multiplication* of the living virus and those due to *sensitivity* to the virus, dead or alive, and its products—and, it might be added, sensitivity to the tissues of the animal from which the vaccine lymph is prepared. Unvaccinated persons and those whose immunity from previous vaccination has lapsed respond with the characteristic primary type of reaction, which is maximal between the seventh and tenth days. Those with some residual immunity respond with a modified lesion which runs its course rapidly and reaches its maximum intensity between the third and seventh days; this reaction is usually called vaccinoid or accelerated. Mitman, however, maintains that the term "accelerated" is a misnomer, since in his view the impression of acceleration is due to an early sensitivity reaction: the onset of the modified reaction may even be slightly delayed. Since, in fact, this reaction reaches its maximum before the seventh day there are many who will still consider that the term "accelerated" is a fair description.

The sensitive person, whether susceptible or immune, responds to the virus, dead or alive, with an early reaction on the second or third day: this has been called the immediate reaction of immunity, but it is neither immediate nor a reaction of immunity. It may occur in those whose immunity has completely lapsed, and, since sensitivity persists after immunity wanes, revaccination may result in a combined early and vaccinoid reaction. Vesiculation may occur in sharp early reactions, but the vesicle differs clinically from the true vaccinial vesicle: it is usually very small, does not spread laterally, is itchy and easily ruptured, and leaves no scar. The early reaction is not an indication of immunity, although it may occur in those who are immune; it is evidence only of previous sensitization to the virus or to the animal proteins in the lymph. Mitman could obtain no evidence that exceptionally severe early reactions were due to the quality of the lymph used.

No reaction at all has been regarded as evidence of complete immunity, but is more commonly due to errors of technique or relatively inactive lymph. Mitman shows that technical failures can occur with surprising frequency even in the hands of experienced vaccinators. Although it is true that no reaction may be obtained in highly immune people who have been relatively recently vaccinated, absence of reaction should never be accepted as evidence of immunity without repeated revaccination with a lymph proved to be potent in susceptible subjects vaccinated at the same time. Mitman reports that severe local reactions and general disturbance due to secondary infection of the vaccinial pustule can be reduced by the use of penicillin tulle gras dressings and that this does not affect the development of immunity, since the virus is not sensitive to penicillin.

[1] *Mon. Bull. Minist. Hlth, Lond.*, 1952, **2**, 100.

THE RAILWAY DISASTER

Serious accidents on the railways of this country are fortunately very uncommon, so that the occurrence of such a major disaster as the one at Harrow and Wealdstone station came as a great shock to the public mind. Everyone has been filled with admiration for the promptness and devotion shown by the various rescue parties,

and the thanks of the community are particularly due to the medical unit of the American Air Force which rendered such signal service to the wounded. It was in no sense of carping criticism, therefore, that the two letters were written which appear in our correspondence columns this week. After every such emergency it is wise to review the procedure adopted in bringing first aid to the injured and to search thoroughly for any, even the slightest, weakness in the arrangements provided.

Our correspondents call attention to one matter of major policy and several minor details of treatment. The major question is whether there should be a system throughout the country whereby, in case of sudden emergency or serious accident, a fully equipped surgical (or medical) unit could on request always be promptly dispatched to the site of the disaster. Such units could be based on the nearest large hospital, and the arrangements would have to be made through the chief hospital centre for the area or region so that sufficient help might be sent and yet no undue overlapping occur. In the case of the Harrow disaster many hospitals were notified that they might have to receive casualties, and some stood by for a long while before being told that they would no longer be wanted to receive them. There was a precedent for such surgical units during the war, when surgeons and surgical equipment were dispatched urgently to places where surgical aid was suddenly called for. It might be argued that such units would seldom be needed, and that it would be waste of time to set up an organization which would only occasionally be required; but a skeleton service of such a nature would be of the greatest help if the threat of war ever became serious again.

The minor questions of treatment concern the injection of morphine, the giving of transfusions before the patient is sent to hospital, and the administering of drinks to those who are able to take them. Certainly it should be a routine practice for those who inject any morphine (either subcutaneously or intravenously) to indicate in some manner and on some substance which cannot be detached from the patient the exact dose which has been administered and the time of injection. Whether a transfusion should be given to a patient before he reaches hospital should depend on the judgment of the skilled surgeon who sees the patient. The giving of tea or other drinks is contraindicated if there is the slightest suggestion or possibility of any injury to the abdominal contents, but otherwise there would not appear to be any serious objection.

GROWTH OF CHILDREN

Aberdeen University Court is to be congratulated on publishing records of the growth of children from birth to 5 years of age made by the late Professor Alexander Low,[1] anatomist and anthropologist. The absence in Britain of measurements of the same children over a period of years—so-called velocity or longitudinal studies—has often been lamented in these columns[2] and in the general literature. There was perhaps a despondent sigh in our comment last year, "Unfortunately such longitudinal surveys are slow and laborious."[3] Tanner[4] has drawn attention to the astonishing fact that hitherto there have been no British standards for any anthropometric characters except height and weight, and has insisted that "all anthropometric measurements, including height and weight, need considerable care and effort in the taking, and unless done properly are not merely useless but confusing." It is seldom that authors state explicitly their methods of measurement and the exact points used, a circumstance that renders comparative assessment of data in different papers exasperating and often futile. The Aberdeen figures are informative and remarkable in that the methods of measurement have been carefully described and carried out by means of some 20,000 observations by the same person, an experienced anatomist and anthropologist, recording the growth of 66 boys and 60 girls at the ages of 3 days and 1, 2, 3, 4, and 5 years. They were all normal children of north-east of Scotland stock. The careful nature of the work may be judged from the measurements included: weight, head length, breadth, height, and circumference; face length and breadth; nasion–alveolus; chin–occiput; standing, sitting, suprasternal, umbilical, and pubic height; mid-fingertip height; trunk length; bisacromial width; bitrochanteric width; foot length; chest circumference; anterior fontanelle; number of teeth; length of left cubit; cephalic and facial indices; sitting–standing ratios; weight–height ratios and chest-girth ratios. Also recorded was such general information as the ages of the parents, number of pregnancy, month of cutting first tooth, and whether bottle- or breast-fed. Some writers state that the circumference of the calf is a good measure of muscular development, and it is interesting that Low has not included this in his list. Anatomists teach that the longer the leg lever the less the calf, and anthropologists state that thick calves are characteristic of Europeans and thin calves of the darker races. Possibly the calf is not the reliable measure it might at first appear.

According to the foreword by colleagues well aware of Professor Low's convictions, he profoundly disagreed with the current statement that children of to-day are taller and heavier than formerly; he maintained that, however excellent the nutrition received by certain children, they would not grow beyond the size of their type, and he was convinced that even if food was poor, provided a child got sufficient, it would reach the stature for its particular stock. When we reflect that this serious statement was made by one who at least had gathered the facts we may in turn have serious reflections on public expenditure and political claims made on inadequate data.

To have followed these children up to 5 years must surely have required a deal of patience, tact, and tenacity. From this age onwards it may be within the province of the school medical services to further the study. Certainly workers in this field now possess reliable velocity records of growth during the first five years of life.

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[1] *Growth of Children, 66 Boys and 60 Girls Each Measured at Three Days and at One, Two, Three, Four and Five Years of Age.* University of Aberdeen. 1952 10s.

[2] *British Medical Journal*, 1952, 1, 963.

[3] Ibid., 1951, 1, 403.

[4] *Arch. Dis. Childh.*, 1952, 27, 10.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

VERTIGO

BY

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Vertigo is a common and often disturbing symptom in which the senses are deceived into seeing or feeling movement. The patient is likely to refer to this hallucination of movement as "giddiness" or, if slight, "dizziness." Although the term "vertigo" suggests by derivation a "turning," it can quite properly be applied to apparent movement in any direction. There is no need to postulate a turning or whirling movement, nor in consequence is it necessary to add the terms "true" or "false." Vertigo is always accompanied by a disturbance of balance which usually causes the sufferer to seek support, and if sudden and severe may throw him to the ground. It may even occur at rest, making him clutch at his chair or the bedclothes for added support. Vague disturbances of balance without any sensation of movement, particularly when associated with heights, flights of stairs, and edges of railway platforms, are rarely accompanied by signs of organic disease and should not be called vertigo.

Though the symptom of vertigo leads so often to an inquiry into the efficiency of the cardiovascular system, the digestion, the condition of the eyes, and even the state of the endocrine organs, it will be found that in most cases of severe vertigo some part of the vestibular system is at fault. If the central nervous system is normal a cause of the vertigo is likely to be found in the peripheral part of the vestibular system in the labyrinth or eighth nerve. This is not really surprising when we recall that the vestibular apparatus in the labyrinth is the receptor organ for the sense of balance. As long ago as 1893 Gowers in his *Diseases of the Nervous System* observed :

> "Of 106 consecutive cases in which definite vertigo made the patient seek advice, in no less than 94, ear symptoms were present. . . . We have seen that it is exceedingly rare for definite vertigo to occur apart from aural symptoms, and it is certain that, in the majority of cases in which such vertigo has been ascribed to other causes, these have only had an exciting influence, and the symptom has been essentially due to the effect of unobtrusive labyrinthine disease."

The Vestibular System

As, therefore, vertigo so often implies some interference with the proper working of the vestibular system, either within the labyrinth or with its central connexions in the brain, it will be useful at this stage to refer briefly to the form and function of this system. It includes the vestibular end-organ housed in the posterior part of the labyrinth, the vestibular division of the eighth nerve, and the extensive central connexions in the brain stem with the cerebellum, the nuclei of the eye muscles, and the vestibulo-spinal tract of the spinal cord. The vestibular nuclei in the brain stem lie near the vagal centres, and it is not surprising to find that a prominent, disturbing, and often misleading feature of a vestibular disorder is the vagal effect which is discussed below.

The vestibular end-organ in the higher orders of the animal kingdom shares the bony labyrinth with the organ of hearing ; consequently deafness, tinnitus, and vertigo are often seen together and usually indicate a labyrinthine disorder.

In normal circumstances man is not accustomed to using his labyrinths for balancing. He finds that with his feet firmly planted on the ground in well-lighted surroundings visual and skin-muscle-joint impressions enable him to balance without his labyrinth. This is why, when he has to use it, as when swimming or riding a bicycle, he feels insecure until he has had plenty of practice.

Here then is an elaborate and delicate sense organ which in our waking and moving hours is constantly receiving and transmitting impressions of the very existence of which we are quite unaware, until it goes wrong. Its object is to assist in maintaining balance by stabilizing the position of the eyes, head, and body in that order of importance. It reacts to the slightest movement or change in posture either by a movement of the fluid endolymph in the semicircular canals or by a shift of the otoliths. Impulses are constantly flowing up each vestibular nerve in such a manner as to balance one another, travelling to the eye nuclei, to the cerebellum, and to the body muscles without impinging upon consciousness.

Acute Vestibular Failure

Any lack of harmony between the two labyrinths will result in a disturbance of balance, and the most severe upset will follow sudden and complete loss of function on one side. The effect of this can be summarized as follows :

(1) *Vertigo.*—Objects appear to move in one direction and the subject feels he is moving or turning in the opposite direction.

(2) *Nystagmus.*—The eyes move slowly in one direction and quickly flick back to their former position. This alternate and rhythmic oscillation of the eyes may be rotary, horizontal, or vertical.

(3) *Overbalancing.*—The patient falls or deviates in the direction of the apparent movement (which is towards the affected labyrinth).

(4) *Vagal.*—Under this heading are included the variable and often misleading associated features of excessive endolymph movement, or of sudden and severe interference with the normal stream of impulses from one or other labyrinth. The pallor, nausea, and vomiting, the slow thready pulse, and the fall of blood pressure are all due to a disturbance spreading from the vestibular nuclei in the brain stem to adjacent vagal centres. Additional features of such a disturbance may include epigastric pain from vomiting on an empty stomach, activity of the biliary apparatus resulting in the vomiting of bile, and in an unfortunate few excessive intestinal movement causing diarrhoea.

The sudden failure of one labyrinth may be likened to the effect produced when one engine of a twin-engined aeroplane fails. The plane is driven round by the normally running engine and great confusion may ensue before, by suitable adjustments to the controls, the pilot is able to bring the plane back to its former course. He will, in all probability, be able to hold it more or less on a straight course, though at first this may be difficult and even tiring. In some respects an even more disturbing event would be if the defective engine, rather than stopping altogether, spluttered and functioned intermittently or gave out when the nose of the plane was pushed up or down.

The same sort of thing happens in man with sudden vestibular failure on one side. This is followed by intense vertigo, collapse, nystagmus, and vomiting. These distressing features slowly disappear as central compensation is

established, and after some days the patient is able to creep cautiously about and gradually to regain his balance. If, however, the labyrinth fails only momentarily or with the head in a certain position, the effect should not be so devastating and may last only a few minutes or hours. Nevertheless, these attacks, if recurrent, may engender such a feeling of insecurity that the sufferer may feel compelled to limit his activities.

These effects take place when the vestibular end-organs in the labyrinth have been overstimulated by excessive movement, as in motion sickness, or when normal activity is impaired as the result of injury or disease affecting one or other labyrinth. In the extreme case of sudden and complete unilateral vestibular failure the effect is startling, and it may be difficult to persuade the patient, his friends, and even his medical attendant that a disordered labyrinth is responsible for all the trouble.

Actually the overwhelming giddiness, the awful sickness, and the turbulent eye movement—all enhanced by the slightest movement of the head—that accompany acute vestibular failure form a picture of helpless misery that has few parallels in the whole field of injury or disease.

This lurid clinical scene, typical though it is of acute vestibular failure, as a rule only follows sudden and complete loss of function in a previously active end-organ. When the lesion is incomplete, and particularly when it is gradual in onset, the symptoms are less intense.

Diagnosis

Vertigo is such a disturbing complaint that both patient and doctor will naturally wonder whether there is any serious underlying cause for the trouble. Though custom has led to the earliest inquiries being made into the state of the cardiovascular and digestive systems, it will be found that when vertigo is a prominent symptom these systems are rarely affected, though in cardiovascular disease minor forms of dizziness are often encountered. The visual hallucination of movement may lead to the suspicion of an ocular cause, though here again the eyes are usually innocent. The menopause may sometimes be held responsible because of the transient dizziness that is often experienced at this time.

This leaves the central nervous system, including the vestibular nerve and the vestibular end-organ in the labyrinth, as possible sites for disease causing vertigo. As it is necessary to find out whether there is any serious underlying cause for the vertigo it will be convenient to consider first of all the causes for vertigo that may be found within the central nervous system.

Central Vertigo

Any involvement of the central vestibular connexions, particularly if it is sudden, may lead to vertigo. The most likely causes are a vascular lesion or a patch of sclerosis. Tumours, being more gradual in their onset, are not so likely to produce severe vertigo. These disorders are rarely limited to the vestibular tracts in the central nervous system, so that associated symptoms will suggest the true nature of the condition. In disseminated sclerosis the picture may sometimes be one of acute vestibular failure, but there is usually some accompanying sensory disturbance and diplopia. An epileptic fit may be preceded by a vertiginous aura, but loss of consciousness, which is rarely seen in labyrinthine vertigo, offers a clue to the cause. Tumours in the posterior cranial fossa, particularly if they involve the roof nuclei in the cerebellum, may cause postural vertigo and nystagmus; whilst tumours pressing on the vestibular nuclei in the brain stem will usually cause nystagmus and a varying degree of dizziness. The commonest of these tumours is a neurofibroma of the acoustic nerve, and though the vestibular nerve is always involved, with loss of peripheral vestibular function, vertigo is rarely a prominent symptom, probably because the gradual loss of vestibular function has enabled compensation to take place. Arachnoiditis in the posterior fossa may be the reason for vertigo and it may simulate an acoustic neurofibroma.

Thus when vertigo is associated with loss of consciousness, diplopia, sensory disturbances, failing vision, incoordination of movements, or persistent spontaneous nystagmus, it is necessary to search for a possible cause within the central nervous system. Spontaneous nystagmus due to a labyrinthine lesion never lasts for more than three weeks, and a vertical nystagmus always means a lesion within the central nervous system. Apart from an acoustic neurofibroma, it is unusual, though not impossible, for deafness to be associated with vertigo due to central causes.

Peripheral Vertigo

Most of the patients in whom severe vertigo is the presenting symptom will be found to have a lesion in the peripheral part of the vestibular system, usually within the labyrinth. It has been customary to refer to this group as aural vertigo, or Ménière's syndrome, in honour of the French physician who first drew attention to the labyrinth as the seat of the disorder responsible for paroxysmal attacks of vertigo usually accompanied by unilateral deafness and tinnitus. Attacks of vertigo without deafness earned the sobriquet pseudo-Ménière's syndrome. Under these headings there has been grouped, irrespective of their pathology, a variety of conditions, most of them otological, and it will be useful to consider them under headings based on their pathology.

Hydrops of the Labyrinth.—Hallpike and Cairns in 1938 found that the pathological process responsible for paroxysmal attacks of vertigo accompanied by unilateral deafness and tinnitus, where the ears appeared normal and there were no signs of disease within the central nervous system, was an obstructive distension of the endolymphatic system. They called this Ménière's disease, and the additional descriptive subtitle of endolymphatic hydrops has since been added. The sexes are equally affected, and in more than half the cases the symptoms first appear before the age of 50. The attacks of vertigo may be preceded by deafness and tinnitus or may occur without warning and at any time, even when asleep. The vertigo can be violent and may last for some hours, often being accompanied by severe vomiting. After a rest and possibly a good sleep, recovery is the rule. Attacks often occur in groups at intervals of days or weeks with periods of complete freedom for months or years. The hearing in the affected ear is usually and significantly distorted so that loud, musical, and high-pitched sounds are distressing. When examination reveals a normal-looking auditory apparatus but perceptive (nerve) deafness and an impaired response to a caloric test of vestibular function, without any sign of disease within the central nervous system, the diagnosis of hydrops is established. A careful examination of both cochlear and vestibular function is necessary to locate the lesion, which is usually in one labyrinth, though in about 15% of cases both are obviously affected.

Injury.—The labyrinth is very susceptible to damage in a head injury, either by a skull fracture involving the labyrinth or following severe concussion when the delicate membranous labyrinth is shaken up and suffers damage which may be permanent. That is why giddiness is a prominent feature of the post-concussion syndrome and of some basal skull fractures. In such cases examination will usually reveal a vestibular defect. After the obvious effects of the injury have passed off persistent dizziness and a disturbance of balance should lead to a suspicion of vestibular damage, even if there is no deafness. In some cases vertigo may be induced or aggravated by movements of the head or by holding the head in a certain position, usually backwards and to one side.

Infection.—In labyrinthitis secondary to otitis media the infection will spread inwards, either through natural preformed spaces in acute infections or more commonly by erosion of the bony labyrinth in chronic suppuration. In the latter event the final invasion may be preceded for some time by slight dizziness which is accentuated by pressure on the ear, the so-called fistula sign. This warning sign in chronic suppurative otitis media calls for early operative treatment if the labyrinth and sometimes life are to be saved. Once the labyrinth is invaded by infection all the features of acute labyrinthine failure will be present, and will be likely to continue for some days. There will also be some accompanying fever and constitutional disturbance, with the prospect of the infection spreading to the meninges. In *meningococcal meningitis*, infection may spread outwards from the meninges to the labyrinth, though this complication is often overlooked at the time because of the severity of the meningitis, and it may be revealed only by residual deafness and some disturbance of

balance. Unfortunately neurolabyrinthitis is often bilateral, in which case total deafness results. *Mumps* may also be complicated by neurolabyrinthitis, though here fortunately only one labyrinth is likely to be affected. Here, again, the symptoms of acute labyrinthine failure are usually attributed to the causal infection. In another small group there are signs of acute vestibular failure accompanied by facial palsy and possibly a vesicular eruption around the affected ear, the so-called *geniculate herpes* or Ramsay Hunt syndrome.

Toxic.—The vestibular system is undoubtedly vulnerable to certain toxins, in particular to streptomycin. This may cause permanent impairment of vestibular function, both labyrinths usually being affected. In an effort to overcome this selective toxic action of streptomycin, the dihydro compound was introduced. Unfortunately this has proved to have a similar effect on the cochlear apparatus, so it seems that until a non-toxic compound has been found it is wiser to use the original brand cautiously, as it is obviously better to be giddy than deaf. In another and not uncommon group there is a sudden and inexplicable loss of vestibular function on one side, with all the clinical features of acute vestibular failure. Hearing is unaffected, and it seems that the site of the lesion is somewhere in the vestibular neurons. Dix and Hallpike refer to this condition as *vestibular neuronitis*, and they have found that in a proportion of cases there is an active focus of sepsis which may be responsible. The condition is easily recognized as one of acute vestibular failure by the sudden onset of severe vertigo accompanied usually by vomiting, which demands absolute rest in bed, as the slightest movement of the head or body causes further vertigo. The symptoms slowly subside over the days, and after two or three weeks all is well apart from a little residual dizziness with sudden movements of the head. It is probably the cause of so-called "epidemic labyrinthitis," though in many cases there is no evidence of an infection.

Paroxysmal Positional Vertigo.—In this group of cases vertigo is induced only with the head in a certain position, usually when it is placed backwards and to one side. It will be found that in such cases the paroxysm of vertigo lasts only a few seconds, and does not reappear for at least half an hour, even when the offending position is resumed. Dix and Hallpike have found a lesion in the utricular labyrinth in such a case. This condition is benign and may disappear after a few months. In some cases there is a history of a head injury while in others a focus of sepsis has been demonstrated. It has to be distinguished from the central form in which fatigue does not occur.

Some idea of the relative frequency of these different causes of vertigo can be gained from the following figures, which show the various cases in a series of 1,523 patients referred for an otological examination because of vertigo :

Central		107
Peripheral		1,349
Hydrops	972	
Trauma	123	
Vestibular neuronitis	109	
Positional	84	
Infective	61	
Not Classified		67

It will be appreciated that the proportion of central cases in this series is smaller than a general neurological experience would suggest, though it corresponds with Gowers's findings.

Management

The first step in the management of a case of vertigo is to exclude, if possible, any central cause. If this can be done, then it is important to ensure that the patient appreciates that the underlying cause of the condition is benign. If the explanation offered is acceptable—and it is usually thankfully received—it dispels many fears and doubts and is an important step in rehabilitating the patient.

Any infective ear condition must be dealt with, while for the remainder it is important to get and to keep them moving once the acute stage is past. Special balancing exercises are invaluable for traumatic cases, and these are most successful when carried out in a class.

During an attack of acute vestibular failure absolute rest and strong sedatives are needed. Vomiting may call for an injection, the most effective being inj. phenobarbiton. sod. 3 gr. (0.2 g.). In Ménière's disease a course of one of the barbiturates, though it does not have any specific effect, has a generally calming influence, and to a certain extent modifies the attacks. Certain seasick remedies containing hyoscine or an antihistaminic may be very useful in modifying the severity of the attacks, and are often helpful in traumatic cases in which the dizziness may be more or less constant.

In Ménière's disease a serious attempt should be made to limit the intake of sodium, and a low sodium diet should be ordered. Discouraging the retention of fluid within the body often seems to ward off attacks. In the hope of influencing the blood supply of the labyrinth histamine, nicotinic acid, and operations on or injections into the cervical sympathetic are sometimes tried. Such measures may help some cases, but it is difficult to assess the value of any conservative treatment in a condition such as hydrops of the labyrinth in which long periods of spontaneous remission are apt to occur. When the attacks are not controlled by conservative measures, and when the disease is unilateral and the hearing is badly affected, some form of operation on the labyrinth may have to be considered. Opening the bony external semicircular canal and removing a portion of the membranous labyrinth is enough, in Ménière's disease, to destroy all function and prevent any further attacks from that labyrinth. It is simple in terms of general surgical principles, there need not be any complications, and recovery is quick.

In bilateral cases, and when the hearing in the affected ear is still useful, intracranial section of the vestibular nerve may be considered, though of course this is a more extensive and potentially a more serious operation than labyrinthectomy. Deliberate intoxication of the vestibular labyrinth with streptomycin has been advocated, but experience suggests that in some instances the cure may be worse than the disease, and such a form of treatment should be considered only in relatively young patients in whom the condition is bilateral.

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NURSE-TRAINING SCHEME FOR EX-TUBERCULOSIS PATIENTS

BY

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There are probably very few sanatoria which do not employ some ex-patients on their staff, and no doubt many have already developed their own schemes for employing ex-patients as nurses. The experience of the scheme at Creaton Sanatorium, Northamptonshire, may be of interest to those concerned with tuberculosis and the administration of sanatoria.

There are 152 beds at Creaton Sanatorium, 91 for males and 61 for females. The establishment allows for 40 on the nursing staff, but the total number of nurses employed is at present 34. When investigating the possibility of meeting the nursing shortage by the employment of ex-tuberculosis patients we found that though a valuable contribution to staffing difficulties was made by the casual or incidental employment, in various capacities, of ex-tuberculosis patients, much better results, both for the sanatorium and for the ex-patient, could be anticipated if employment were put upon a more regular and permanent basis. Further, although it was probable that without any action at all by the sanatorium authorities a few ex-patients would seek employment

there, it was almost certain that this number would be increased if a specific scheme were in operation and an active, intelligent, and continuing interest taken in it by all concerned.

The following summary of the final report which was adopted by the hospital management committee will give an indication of the scheme now actually in operation.

Selection

Patients of both sexes could participate in the scheme, though it was felt that females would probably outnumber males. There were no age limits, though younger patients would tend to be more attracted than the older ones. Consideration could be given to patients who were no longer infectious and who were otherwise suitable, and it was estimated that perhaps some 2% of all patients could be regarded as potentially eligible for the scheme.

The suitability of patients would be a matter for the ward sister, almoner, matron, and consultant physician, though it would be left to the two latter officers to make the final decision. Those who appeared to be suitable would be told the outlines of the scheme and given time to think the matter over. Those who were interested would, at the appropriate time, be enrolled for a probationary period of approximately three months upon a part-time basis of from 12 to 30 hours a week. There would be no general publicity regarding the scheme, as this might lead to distress on the part of patients who wished to participate but for medical or other reasons were not suitable.

Training

It was emphasized that the training of ex-patients (for the Tuberculosis Association certificate) was an essential part of the scheme, rather than their mere employment, and it was early recognized that the strain of the three-months intensive course of lectures for the preliminary State certificate presented a real difficulty. This was overcome by arranging that the course of lectures should in fact be taken over a period of nine months, and, as these lectures were taken at the Group General Hospital, arrangements were made for ex-tuberculosis student nurses to take half the lectures in one three-months course, to take no lectures for the next three months, and then to take the other half of the lectures in the next three-months course.

The strain of practical experience during the first year of enrolment was also mitigated for the ex-patient student nurse by concentrating entirely upon the tuition aspect of her ward work and requiring from her no element of contribution to the normal routine work of the sanatorium, such as would be required in the normal course of events from nurses in training. In these ways it was estimated that an ex-patient student nurse should be able to take her preliminary certificate within 15 months of enrolment, while working a 36-hour week as compared with the 48-hour week of the normal student nurse. The final T.A. certificate could be taken one year later, so that the ex-patient student nurse would again be able to devote all her energies to acquiring experience necessary for the certificate rather than to contributing fully to the work of the sanatorium.

It was suggested that, once she had secured her T.A. certificate and was able to work full time or nearly full time, the ex-patient nurse should be eligible for promotion to staff nurse, ward sister, and eventually administrative sister in open competition with other nurses suitably qualified. There seemed to be no practical or legal reason why nurses holding only the T.A. certificate should not act as ward sisters in sanatoria, provided a senior officer with the S.R.N. qualification was always available.

At all stages the ex-patient student should be subject to adequate medical supervision, and she should be encouraged to report if she became over-tired. Care would be necessary to ensure that students did not overtax themselves, but, on the other hand, they must be encouraged to think of themselves as approaching a complete return to normal life.

From first to last there must be the clearest recognition that the scheme depends entirely upon part-time work, and there must be no disposition to regard this as an inconvenient temporary arrangement. The amount of time to be worked must be carefully assessed, and, if necessary, modified from time to time by the consultant physician.

The original scheme envisaged that all ex-patient trainees subject to it would be resident, and there is no doubt that this is preferable if at all possible. Immediately upon enrolment, and for some months thereafter, accommodation separate from the permanent staff of the sanatorium is desirable from all points of view, but few sanatoria have such separate accommodation readily available, and its special provision is at the moment out of the question. In the light of experience the scheme was accordingly modified to permit non-resident students to participate, and this has worked quite successfully.

Salary and Superannuation

Salary scales are those laid down by the appropriate Whitley Council for T.A. certificate-holders and trainees, with pro-rata adjustment according to the time worked. This adjustment is applied to board and lodging repayment as well as to remuneration.

Superannuation could have proved a difficult problem, as there could have been no pretence that ex-patients were being fully rehabilitated and offered a career if they could not have been given superannuation rights similar to those of other employees. The very clear and helpful wording of circular H.M.C. (48) 79 of December 31, 1948, removed any difficulties there might have been on this account. This circular amended the terms previously required of medical certification in connexion with superannuation, so that the form of medical certificate now required to secure entry to the superannuation scheme need merely state that the candidate "is free from any physical defect or disease which now impairs his capacity satisfactorily to undertake the duties of the post for which he is a candidate." Such a certificate can obviously quite honestly be given to any ex-patient nurse whose condition is quiescent and non-infectious and who has reached the stage of working full-time or nearly so. The wording of the circular was clearly designed to include ex-tuberculosis patients (it is specifically so stated in its first paragraph), and it would indeed have been a most unfair discrimination against such employees if the physician's knowledge of their past history and calculation of any possible future breakdown had prevented the issue of a certificate and thus inclusion in the superannuation scheme.

Conclusions

The scheme has now been in operation for approximately two years, and there are at the moment seven student nurses recruited from ex-patients under its terms. This figure represents 1.5% (2% if ward orderlies, etc., are included) of patients passing through the sanatorium during the period of operation of the scheme, and is fairly close to the estimate originally made. Neighbouring chest clinics and sanatoria were informed of the scheme, and one or two recruits were obtained through the clinics, the decision whether or not to enrol within the scheme being that of the sanatorium chest physician in all cases.

The seven ex-patient student nurses are members of a total complement of 12 student nurses, so that the normal recruitment level of the sanatorium, without the assistance of the scheme, would have undoubtedly meant the closing of beds. In addition to the seven trainees within the scheme, there are two ex-patient ward orderlies and one ex-patient staff nurse to whom the scheme applies, but who had been discharged from the sanatorium before its inception.

I am greatly indebted to Miss C. E. Nelson, matron of Northampton General Hospital, for instituting the modified courses of lectures and training; to Dr. E. T. W. Starkie for his advice and great interest; and particularly to Mr. S. G. Hill, LL.B., for his guidance in all questions of legality and propriety under the National Health Service.

THE NEW ACADEMIC YEAR

CHARING CROSS HOSPITAL MEDICAL SCHOOL

In presiding at the inauguration of the new session at Charing Cross Hospital Medical School on October 10, Lord INMAN announced that within the past few days the contract had been signed for the site of the new "Charing Cross" at Northwick Park, near Harrow. Forty-seven acres, he said, had been acquired, of which just upon 34 acres would be used for the hospital and the remainder for the medical school. Thanks to Professor Vines and his colleagues on the planning committee, the plans were all ready, and Lord Inman hoped that it would not be long before the economic position of the country would enable a start to be made on the new scheme.

The Educated Man with a Vocation

A witty inaugural address was delivered by Lord ELTON, after Lady Elton had distributed the prizes. He remarked that the students were in a borderland in the sense that they were both continuing their education and embarking on their career. When he and his fellow students had left Oxford or Cambridge or London they thought they knew all the answers; now they knew that they were just beginning to understand the questions. Lord Elton defined the hallmark of the educated man as possession of the art of readily perceiving the relevant in any complex of facts. The sifting of the relevant from the less relevant was the fundamental intellectual process of any profession. The effective doctor was the one who most accurately detected among many symptoms the one which was of chief importance.

Their patients, he reminded his listeners, were not merely a physical structure. A patient would be a spirit for infinitely longer than he would be a body. Spirit and body acted upon each other, and he was convinced that it was the spirit which exercised supreme control. He had seen many of his colleagues who had died because—whatever their death certificate might have said—they were no longer interested in life. Duodenal ulcer had been found to be due to a person permitting his ego to become too central in his universe. Lord Elton thought that medicine would make more discoveries of this kind.

The really valuable lessons of school and college were the lessons which the student did not know he had learnt and which his teachers did not know they had taught him. Lord Elton hoped that the students would find out that they had a vocation. "Vocation" meant a calling in the strictest and deepest sense; a man received a call from beyond life, as Paul received a call on the road to Damascus. Happiness was a result of performing one's true function; it could never be won by deliberate seeking. A man who had a vocation would always be happy, because his work would release him from the unconscious torment of over-preoccupation with himself.

INTERNATIONAL CONGRESS ON NUTRITIONAL RESEARCH

In 1946 delegates from many parts of Europe were invited to London, under the auspices of the Nutrition Society and the British Council, to report on the food shortages experienced by their countries during the war. At this conference the formation of an International Union between the nutrition societies of various lands was proposed, and it was left to Dr. L. J. Harris to bring it into existence. Business meetings were convened in various parts of the world, and the approval of the United Nations Organization for the project was obtained. A further impetus to international co-operation has now been given by a second scientific conference on "Present Problems in Nutritional Research," organized at Basle from October 1–4 by Professor F. Verzár and attended by 150 delegates from 18 countries. The discussion dealt with the physiology and biochemistry of nutrition, food production and consumption, the control of food adulteration, and the roles of proteins, fats, vitamins, and minerals in nutrition.

Food Production and Consumption

Professor A. I. VIRTANEN (Helsinki) discussed the importance of agriculture in providing for the world's increasing population. In America experiments had been made on the production of proteins, carbohydrates, and fats by means of rapidly growing algae. Much could still be gained, however, by the improved cultivation of land plants. In Ireland, for example, the damp climate was unsuitable for hay-making. As in many other parts of Europe the nutrition of cows and the production of milk could be much improved by making silage, for which he had devised an effective method. Dr. J. TRÉMOLIÈRES (Paris) produced statistics showing that the consumption of foodstuffs in different parts of France varied greatly between districts and between early records and more recent observations. The physiology of digestion in the ruminant, the fundamental basis for the production of milk, beef, and mutton, was described by Dr. D. P. CUTHBERTSON (Aberdeen). Remarkable data on the effect of diet on muscular stamina were reported by Professor H. KRAUT. In groups of German workers or students stamina was subnormal when the diet provided less than about 1 g. of protein per kg. of body weight daily. Professor E. J. BIGWOOD (Brussels) described the analysis of dietary proteins into their constituent amino-acids by means of chromatography on ion-exchange resins. Professor K. LANG (Mainz) described the causes of the loss in nutritive value which occurs when proteins are stored or strongly heated with sugars.

Interesting papers were given by Professor E. ABRAMSON (Sweden) and Professor O. HÖGL (Bern) on the control of the adulteration and sophistication of foods. The inauguration of a central laboratory for the investigation of the toxicity of chemicals used in food manufacture, and for sanctioning the use of chemicals proved harmless, was strongly advocated. Mr. A. L. BACHARACH (London), however, considered that the best safeguard was the caution and integrity of advisory food chemists, backed by the accumulated knowledge of their organizations. Dr. W. R. AYKROYD described the origin of the Food and Agriculture Organization of the United Nations.

Dietary Constituents

Investigations have long been in progress in Germany on the possibility of converting paraffin wax and various waste materials into fats suitable for food. Professor K. THOMAS (Göttingen) explained the effect of the presence of methyl groups and of branched chains on the metabolism of these products. Dr. A. SCHURCH described the isolation of a toxic fraction from heated linseed oil, which had been used in America for cooking purposes when adequate supplies of other fat had not been available. According to Professor K. BERNHARD (Basle) the alcohol phytol, a component of chlorophyll, resembles choline in preventing the accumulation of excessive fat in the liver. Professor A. B. L. BEZNAK (Birmingham) described the effect of fat in diets low in vitamin B_1 on the growth of rats both when rested and when exercised.

Dr. L. J. HARRIS (Cambridge) spoke on the practical significance of vitamins in relation to national health policy, with special reference to British experiences in the war and since. He considered vitamin D to be the most important vitamin in this country, as indicated by the decrease in the incidence of rickets since the existence of the vitamin was realized soon after the first world war. From data on food consumption it might be deduced that there had been considerable increases in the intakes of vitamins B_1, C, riboflavin, and nicotinamide between 1939 and 1947. In Britain reliance was placed on a surprisingly small number of foods for the supply of the necessary vitamins. Thus much of our vitamin B_1 came from bread, and the adoption of a high rate of extraction had greatly increased our intake. Vitamin D was derived mainly from vitaminized margarine and

from cod-liver oil. The improving health of the community was reflected in greater weight and height gains in children, and by diminishing mortality and morbidity rates. Professor H. Dam (Copenhagen) gave a full account of the numerous effects of vitamin-E deficiency in various animals, and outlined the complicated interrelationships between the vitamin and other nutrients. Thus cod-liver oil could oppose the action of vitamin E, and could influence the nature of the lesions sustained in avitaminosis. Dr. T. Moore (Cambridge) gave further evidence on Dam's interesting discovery that the dye-stuff methylene blue has some degree of vitamin-E activity. He found that it could protect rats fully against some of the abnormalities caused by vitamin-E deficiency but not against others. Dr. I. Leitch asked whether Professor Dam considered that there was any danger of cod-liver oil being toxic in children, as had already been found in calves. He replied that in his opinion tocopherol should be added to cod-liver oil as a precaution.

Communications on mineral metabolism were given by Professors H. Cremer (Mainz), V. Demole (Lausanne), T. Gordonoff, and A. J. Held. Differences in opinion were expressed on the desirability of adding fluorine to foodstuffs to give protection against the dental caries which is very prevalent in Switzerland. It was held by some speakers that this step might disturb a balance between fluorine and iodine and increase the incidence of thyroid diseases. In discussing the role of hormones in food production Dr. S. J. Folley (Reading) mentioned the influence of iodinized casein or thyroxine on the production of milk. He also dealt with the sex hormones, which may be used *inter alia* to caponize cockerels, and with the pituitary hormones. Dr. S. G. Greenberg (U.S.A.) spoke on the effects of cortisone in decreasing the efficiency of the utilization of food.

The next congress arranged by the International Union of Nutritional Sciences will be held in Amsterdam in the summer of 1954.

THE LAKE DISTRICT MOUNTAIN ACCIDENT COMMITTEE

The development of the Lake District National Park has attracted an increasing number of inexperienced walkers to the area. In consequence there has been an increase in the number of mountain accidents and in the number of persons reported missing on the fells. Over many years there has been a gradual development of first-aid and mountain rescue posts, pioneered by the various climbing organizations, situated almost exclusively in the main rock-climbing areas. These posts are excellently equipped and in addition there are two organized mountain rescue teams based on Coniston and Keswick.

Analysis of recent accidents has shown that an increasing proportion of casualties are drawn from the ranks of fell walkers and hikers as distinct from rock climbers, and it is now locally considered desirable that the provision of first-aid and rescue facilities should be extended to all valleys in the National Park which are at present without them. The aim is to ensure that into whatever valley a person may descend for help there may he find equipment readily available and at least a nucleus of local dalesmen trained in its use.

To achieve this aim a committee has been set up, provisionally named the Lake District Mountain Accident Committee, with representation from the main climbing, rambling, hostel, and holiday organizations, the police, the British Red Cross Society and the Order of St. John, the local county district councils, the Royal Society for the Prevention of Accidents, the Joint Committee on Mountain Accidents, and the Royal Air Force Mountain Rescue Service. The medical officer of health of the combined county districts of Westmorland was appointed the first chairman. The functions of the new committee will be threefold: (1) to co-ordinate and extend the present arrangements for first aid and rescue in mountain accidents of all types; (2) to co-ordinate and improve the arrangements for searching for persons reported missing on the fells; (3) to foster and encourage preventive measures against these accidents.

Search Parties

There have been many recent accidents in which shock and exposure have been material factors in the cause of death. It is felt that lives will be saved and suffering relieved by speedy location of the patient, prompt and adequate first-aid and shock treatment on the site, followed by gentle removal from the fellside to the waiting ambulance in the valley below. Arrangements for searching for persons missing on the fells need improving, because many of the recent fatal cases have been found many miles from where they were presumed to be. Not only must search be made over a wider area, but it must be started more promptly if lives are to be saved during the vital initial 24 hours. It is planned to form additional organized search parties both within the National Park and in the areas within easy travelling distance, and to make fuller use of the extensive resources of the Royal Air Force Mountain Rescue Unit for this purpose, all in close co-operation with the police authorities.

THE HARVEIAN ORATION

LORD MORAN ON QUACKERY

Lord Moran delivered the Harveian Oration at the Royal College of Physicians on October 17. The title of the oration was "Into the Past."

Lord Moran began by reminding his audience that the College had been founded by Henry VIII in 1518 primarily to suppress the swarm of unlicensed practitioners and quacks who were then infesting the country. The war between the College and the quacks had lasted for more than two centuries. In it the Universities of Oxford and Cambridge were non-combatants, and the Court and Church and State were in the main on the side of the quacks. It was not, however, the strength of the opposition that had daunted the College. It had other troubles. For one thing, in trying to unravel the web of human credulity the College was not helped by the fact that people were completely in the dark about how the mind worked—and that was still true at the present time. For another, there was a bit of the quack in most folk, and the College knew, when it set out to change human nature, that it was not likely to suffer from unemployment.

Why People Go to Quacks

Perhaps the College went about things the wrong way. Certainly it showed more aptitude for repressive measures than for getting down to the root of the trouble. No one apparently gave much thought to the task of undermining the hold of the quack on the public mind. After all, why did people go to quacks? It was not reason that took them there, for the College case was unanswerable. It was simply this: that if a man was going to practise as a doctor he should first be trained as such. People went to a quack because they thought he was better than a doctor. He did things and they were impressed.

The only remedy was to teach the public what a good doctor could do. More than one president had tried to wean the public—and sometimes the profession—of their pathetic faith in physical activity, in a doctor who did things, in the giving of a bottle of medicine. William Pitcairn had said that the last thing the physician learnt was when to do nothing, when to leave things to time and Nature. He had pointed out that a popular doctor was not necessarily a good doctor. Nevertheless a popular doctor often helped his patients because he was usually a sound psychologist. There was nothing wrong in that. In trying to make Medicine a science they should never forget that it was also an art. A physician ideally should be both a scientist and an artist.

Impressing the Patient

Perhaps instead of spending so much time and effort in trying to educate the public, it might have been better to begin by educating the profession, by purging the practice of Medicine of all those elements of humbug which have excited the ridicule of every satirist from Molière to Shaw. How could this be done? If the doctor resorted to humbug it was in order to impress the patient. He would cut the cackle when he no longer needed it. And the physician, with his antibiotics, his sulpha drugs, insulin, liver extract, and the like, was now fully armed; he should have no need to impress the patient by more dubious methods.

But the real remedy, in Lord Moran's view, was not to pile up ways of impressing the patient, but to make it unnecessary to win his favour. When the fortunes of the doctor and his advancement in life no longer depended upon the patient's caprice, when the patient was deposed as the final arbiter of the doctor's fate, when in short the physician was independent of his patient, then the battle would be won. The trend of events was helping this evolutionary process. The specialist was devoting more and more of his time to hospital practice, where his work was judged not by patients but by members of his own profession. And the system of merit awards to specialists meant that in the future their promotion would depend less and less on the patients' likes and dislikes and more and more on the verdict of their fellow consultants. The danger in this was that in the cultivation of Medicine as a science the physician might neglect Medicine as an art.

Reports of Societies

"YOUR GOOD HEALTH"

The first meeting of the one hundred and eightieth session of the Medical Society of London was held on October 13 at 11, Chandos Street, W.1. After Sir Cecil Wakeley had proposed a vote of thanks to Mr. A. C. Palmer, the retiring president, Dr. Cuthbert E. Dukes was installed as president for 1952–3 and delivered his presidential address.

To provide material for his address Dr. Dukes had taken the trouble to make notes of conversations with 50 doctors (including 23 Fellows of the Society), 50 non-medical men of a similar age group and social grade, and 40 women, all of whom he asked what they considered to be the reason for their good health. The reason why the number of women did not reach the set 50 was because he soon found that the factors to which women attributed their good health were vastly different from those cited by men. For instance, one woman told him that she attributed her good health to the fact that she had just had a baby, and another to the fact that she had an unsympathetic husband. This latter lady explained that she had painful lumps in different parts of the body, but her husband refused to take any interest in them, and as he was generally right in his judgments about other matters she decided also to ignore these abnormalities. If she had had a sympathetic husband, she said, she would have been a hypochondriac.

The men attributed their good health mainly to one or more of five causes, most frequently to the first two, namely: (1) physical exercise in the open air; (2) congenial occupation (mentioned by several doctors, but seldom by non-medical people); (3) special precautions adopted after a previous illness; (4) temperate habits; and (5) successful emotional adaptation to the strains and stresses of life. Dr. Dukes said that his little bit of research had taught him something which came as a surprise—namely, how little most people thought about health. Personal health was a precious thing, and we had a slight hold on it, and yet those who habitually enjoyed it seldom gave it a thought. He would not say that this was right or wrong; it was only odd. The people who thought most about their health were those who had lost it or those who had suffered from a complaint which was apt to recur.

Time to Relax

A problem which faced most of those engaged in a busy occupation was to achieve relaxation. While periodical breaks such as holidays were indispensable, Dr. Dukes thought that in addition most of them needed also as a daily exercise some means of securing a pause which refreshed and restored the feeling of health and wholeness. If he had charge of the appointment book of some of his friends he would contrive to find a place each day for an entry marked in red ink "Time to relax," by which he meant complete physical, mental, and emotional relaxation, not merely a "few minutes off," though that was better than nothing.

Dr. Dukes also mentioned four forgotten factors which played an important part in good health. The first was the helpful domestic and other environmental influences for which they had occasion to be so grateful. The second was a good inherited constitution—the fortune of being dealt a good hand when one's parental genes were reshuffled in the pack. The third was the firm resolve to keep as well as possible (how easy it was to be ill if one wanted to). The fourth was religion. Only one of the fifty doctors whom he had approached on the subject had spoken spontaneously of religion as of importance in relation to health, but the obvious explanation was that the conversations were not prolonged and intimate enough for such a subject, always approached with diffidence, to be mentioned. It was the "little working bit" of a man's religious faith, not his outward profession or his theological creed, but his inward secret convictions, which ultimately influenced his health to some extent, and might, if given more scope for expression, even improve it.

After the address a vote of thanks to Dr. Dukes was proposed by Mr. V. Zachary Cope and seconded by Mr. J. Johnston Abraham.

A pilot inquiry into some features of general practice was instituted by the General Register Office and the Ministry of Health at the beginning of 1951 (*Monthly Bulletin of the Ministry of Health*, September, 1952). Dr. W. P. D. Logan gives a short account of the inquiry, describing its purpose to discover how far records maintained in general practice might provide information on such subjects as the difficulties most often encountered in general practice, the scope for research there, the causes of ill-health in a particular community, and problems of easy and efficient management. Dr. John Fry, whose study of his own practice appeared in this *Journal* on August 2 (p. 249), has joined this inquiry; the names of other doctors were suggested by regional medical officers of the Ministry of Health. The inquiry has been planned to cover a variety of practices, primarily with a view to seeing whether, for example, size or situation of practice is associated with any particular difficulty in record keeping, to test different methods of recording, and to find out how much, if any, extra trouble would be involved in recording. No attempt has been made to obtain a representative cross-section of general practice, but the inquiry is reported to cover a fairly wide variety of types. While the main object of the inquiry relates to the keeping of records, it also concerns problems of classification and tabulation. The different features of diagnosis the records are designed to show are: (1) illness in relation to the doctor's work (for example, numbers of consultations, certificates issued, and referrals made for various reasons), and (2) illness in relation to the patient (for example, sex and age, and frequency of consultation). The difficulties of obtaining comprehensive and reliable morbidity statistics are well known, and the report points out that if sufficient doctors can provide suitable records these would possibly provide the best source of information for investigating variations in the incidence of disease.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Clinical Tests of "Trilene" Inhalers

Sir,—In response to a recommendation of the Working Party on the Recruitment and Training of Midwives, the Medical Research Council appointed a Committee on Analgesia in Midwifery to satisfy itself that a "trilene" inhaler could be designed which was safe for the use of midwives in domiciliary practice.

Preliminary trials suggest that trilene, administered in new inhalers designed to a performance specification drawn up by the committee, is both safe and effective in normal labour. A sufficient number of the inhalers is now available for more extensive trials, which are being organized, in co-operation with the Central Midwives Board, by a joint subcommittee of the Committee on Analgesia in Midwifery and of the Anaesthetics Committee of the Royal College of Obstetricians and Gynaecologists. The trials have been planned to include the use of the inhalers in domiciliary practice by midwives for selected patients who are expected to have an uncomplicated labour. Certain local health authorities have agreed to take part in these trials, which are being carried out also in hospitals.

General practitioners whose patients would be suitable for inclusion in the trial are being asked, in each case, for their permission. The Medical Research Council will be most grateful for the co-operation of the profession in carrying out these trials.—I am, etc.,

London, S.W.1. GEOFFREY ORGANE,
Secretary, M.R.C. Committee on Analgesia in Midwifery.

Testing Sensitivity to P.A.S.

Sir,—I am receiving inquiries about the method of testing the skin sensitivity to *para*-amino-salicylic acid which was mentioned in Dr. S. J. Steel's article (February 23, p. 415). I thought, therefore, that it would be desirable if I let you have this note on the method employed.

Hard-glass tubing having an internal diameter of 1.0 cm. and a wall thickness of about 0.1 cm. is cut into 2.0-cm. lengths and the cut ends smoothed off in a flame. These glass cylinders are used as the mould for the reagent deposits. The reagents are suspensions or solutions (w/v) of the test substance in chloroform, the mixtures usually being in equimolecular proportions and usually in molar concentrations. The use of more dilute concentrations is usually due to some noxious property of the substance—for example, phenol—which makes it unwise to use the standard concentration. Those substances which form partial suspensions in the concentrations used, such as sodium *para*-amino-salicylate dihydrate, require adequate pulverizing so that an even suspension is obtained. Pipettes, calibrated to deliver the desired quantity, usually 0.1 ml., are prepared with a sufficiently wide-bore tip to deliver the suspensions.

Perhaps I should mention here that the reagents listed in the Table of Dr. Steel's paper were in fact molar concentration mixtures (w/v) in chloroform, the aqueous solution of P.A.S. being 21.1% w/v of the dry dihydrate preparation.

To perform the test, the patient lies face downwards on the bed and the chosen area of the skin of the bared back is wiped with a chloroform-soaked cotton-wool pledget. The precise sites of the proposed reagent applications are now marked out in one of two ways. One way is to press the end of one of the glass cylinders on to an ordinary "office" black-ink pad and then on to the patient's skin, followed by careful rotation of the cylinder, so that finally a series of inked circles are imprinted on the skin. Another way is to mark the skin with an inked pen at a site located by measurement from some bony landmark, the subsequent sites being similarly marked out by measurement from the first site. It is important, however, that the reagent application areas should be accurately known, since non-reactive reagents usually leave no visible mark on the skin at the time of the final observation of the test results. If a series of negative reactions are placed together, there could be some doubt of the identification of the next reacting substance. The circular reagent application areas are conveniently placed in lines parallel to the vertebral column and may extend from buttocks to shoulders. The centres of the circular areas are conveniently placed about 5.5 cm. apart.

The reagents are applied by thoroughly shaking the mixture and rapidly sucking it up into the pipette. The pipette is then rapidly wiped and 0.1 ml. of the contents delivered into one of the glass cylinders being held upright (by an assistant) on the required area of the patient's skin. The chloroform of the mixture in the glass cylinder is now evaporated by directing a stream of gas on to the inner side of the glass cylinder until the reagent deposit on the patient's skin appears either dry (with solid reagents) or oily (with liquid reagents). A convenient source of an appropriate gas in a hospital ward is the standard oxygen cylinder, and the tubing from the oxygen cylinder valve is conveniently attached to the lower portion of a National Blood Transfusion Service transfusion set drip tube, the needle-adaptor making a good nozzle for the gas stream. It is important that the gas stream should not be too rapid and that it should not be directed on to the surface of the reagent mixture lest the mixture splash up on to the sides of the glass cylinder. A different glass cylinder is used for each reagent.

When the reagent has been freed of chloroform, the glass cylinder is given a gentle tap and carefully lifted vertically upwards off the skin, the reagent being left behind either as a solid disk or as a circular oily area. Only a fine trace of the solid reagents should be left attached as a ring at the base of the inside of the glass cylinder. Without disturbing the disk of deposited reagent, each disk is firmly covered over by a single piece of plain adhesive strapping about 5 cm. square. I have not found it satisfactory to cover the whole line of reagent application areas with a single length of strapping, as such strapping may slip several centimetres during the following 24 hours. After the application of the strapping, the patient may continue his normal activities apart from bathing and taking drugs. No discomfort has been complained of apart from a tingling sensation at the time of evaporating the chloroform and a subsequent itching of the skin in the reactive areas.

Twenty-four hours after its application the adhesive strapping is removed, and the reagent material carefully removed from the skin with a gauze swab, and the whole exposed area wiped clean with a damp flannel and gently dried with a towel. Sometimes the reagent application areas need re-marking from the ink pad. The results of the test are recorded now, 24 hours following the reagent application, and again 48 hours following the reagent application. A positive skin reaction is an erythema with or without local skin swelling. A faint erythema, without skin swelling, which is confined to the circular application area is disregarded. The degree of reaction is measured arbitrarily according to the size of the erythema area and to the extent of the skin swelling. When using several reagents, the same observer is able to compare the various reactions in one patient with the various reactions in another patient with a fair degree of reproducibility. It is always advisable to use a control subject and to test both patient and control with plain chloroform and with the marking ink. Rarely, a skin response occurs after a 48-hour interval; I have seen one patient who first showed a feeble reaction to the trihydrochloride–calcium-chloride–streptomycin complex (the concentration on this occasion being 11.6 g./100 ml. chloroform) at the end of the third day following its application.

This method was designed to give a rough quantitative indication of a patient's skin reaction to different chemical substances and it appears to perform this function. Although this method is crude, it readily demonstrates the great sensitivity that some patients' skin has for certain substances. For example, one patient showed a 3.0-cm.-diameter erythema wheal 48 hours after the application of 3-methylamino-phenol. This effect was considered surprising and the test was repeated, with a similar result. The reagent was then investigated, and found to contain traces of a primary aromatic amine. On repeating the test with another sample of methylamino-phenol free of primary aromatic amine, this patient's skin showed no reaction. This example also serves the purpose of emphasizing the absolute necessity for using pure reagents when testing the sensitivity of the skin to drugs. As Dr. Steel suggested, the method is fairly simple and readily performed in a hospital ward without any elaborate apparatus. Furthermore, it gives more controllable results than the more usual method of applying reagent-soaked gauze to the forearm skin, a procedure which may produce severe reactions which are both physically discomfiting to the patient and mentally discomfiting to the physician.

Finally, although the method has been found to be a readily performed and controllable method of skin sensitivity testing to substitution compounds of aniline, benzoic acid, and phenol, and to various other aromatic amines, it may also be useful as a simple tool in the study of the metabolic processes of this type of skin hypersensitivity reaction.—I am, etc.,

Gisborne, New Zealand. A. B. HILL.

Dupuytren's Contracture Treated with Vitamin E

SIR,—Mr. H. J. Richards in his article on "Dupuytren's Contracture Treated with Vitamin E" (June 21, p. 1328) comes to the conclusion that the treatment is valueless. Lest this rather hurried opinion should discourage others from trying vitamin E therapy, may I urge that treatment be given if necessary, and if possible, for at least one year at a dosage of 300 mg. of tocopherol acetate daily?

My first patient was in group II, according to Mr. Richards's grouping. The patient was severely handicapped in that he could not handle pliers, screwdriver, etc. Pain, tenderness, nodules, and thickening of the palmar fascia began to disappear some six months after treatment commenced. He also had local injections of penicillin into the affected palm on one or two occasions. It was necessary to continue dosage for 18 months, by which time the nodules had completely resolved.

The patient takes a maintenance dose of 50 mg. tocopherol acetate daily. If he leaves off this dosage fascial thickening begins to manifest itself a few weeks after cessation of therapy, and he has to resume dosage. He has now been on vitamin E for four years.—I am, etc.,

St. Ann, Jamaica. R. J. DE CARTERET.

Trichlorethylene and Unilateral Amaurosis

SIR,—I have read with interest the details of the case presented by Mr. A. J. B. Goldsmith and Dr. A. J. H. Hewer (October 4, p. 759) and would like to suggest that in this case trichlorethylene should also be taken into consideration as a possible cause of the unilateral amaurosis.

Carden[1] and Humphrey and McClelland[2] give details of cranial-nerve palsies following the use of trichlorethylene. Enderby[3] also reports a case of interference with vision in the right eye. These reports, however, concerned its use in closed-circuit machines, but A. R. Hunter[4] describes several fatal cases following continuous-flow gas, oxygen, and trichlorethylene anaesthesia for radical mastectomy, which at necropsy showed cerebral congestion and softening. Randall (personal communication) also reports another case similarly anaesthetized.

I feel that these complications arising in association with the use of trichlorethylene indicate that this drug should also be taken into consideration by Mr. Goldsmith and Dr. Hewer in discussing the possible causes of the unilateral amaurosis.—I am, etc.,

East Grinstead. JEAN M. HORTON.

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2 Ibid., 1944, 1, 315.
3 Ibid., 1944, 2, 300.
4 *Lancet*, 1949, 1, 1045.

Prolonged Stupor and Anoxic Anaesthesia

SIR,—It is true that nitrous oxide differs from other agents in that it produces its effects largely through replacement of oxygen in the haemoglobin, but there is, I think, abundant evidence to show that, whatever may be the effect of other agents, all forms of general anaesthesia are associated with a reduction of the oxidation processes within the cells, particularly those where there is a large amount of fatty substance, such as the brain cells. Thus, although during the course of any particular kind of anaesthesia the haemoglobin may contain an adequate amount of oxygen, the greater proportion circulates quite uselessly because the brain cells cannot make use of it.

All forms of anaesthesia, then, are in a sense anoxic, and it is a little difficult to understand why nitrous oxide and oxygen, *properly administered*, should be more prone to produce cerebral and lenticular damage than other agents used for general anaesthesia. One can understand that anything leading to congestion within the cerebral circulation, such as an impacted airway, may result in petechial haemorrhages, but is there any evidence to show that this is more likely to happen during nitrous-oxide–oxygen anaesthesia (again I emphasize *properly given*) than during the use of other agents?—I am, etc.,

Aberdeen. A. H. MACKLIN.

Danger from Endotracheal Tubes

SIR,—I, too, have just had a similar experience with a cuffed tube to that reported by your previous correspondents.

The patient was a youth of 16, suffering from a suspected ruptured viscus. An oesophageal tube was passed, and the patient, placed in a 20 degrees head-up tilt, was anaesthetized with thiopentone 0.25 g., succinylcholine chloride 30 mg., followed by spraying the larynx and trachea under direct vision with 4% lignocaine hydrochloride ("xylocaine"). The largest cuffed endotracheal tube possible, a No. 9, was passed, and nitrous oxide 4 litres, oxygen 2 litres, per minute administered, gallamine 100 mg. and pethidine 40 mg. being used to assist controlled respiration. After about 30 minutes control of respiration became difficult and gallamine 20 mg. was given. Complete respiratory obstruction then occurred, with vigorous respiratory movement. The cuff was deflated, which resulted in complete relief of the obstruction. Post-operative bronchoscopy showed no abnormality of the bronchial tree and the patient regained consciousness before leaving the theatre.

There are two points arising from this case. First, the tube was of the new streamlined type, in which the tube underlying the cuff is thinner than the remainder. Secondly, as Dr. W. N. Rollason mentioned (September 13, p. 616), the rise of pressure from room temperature of 15° C. to 37° C. in the air in the cuff will cause an increase of pressure of about 10%. I suggest that, to guard against this difficulty, it is important to select the largest endotracheal tube that will pass the larynx and to use the lowest pressure in the cuff that will produce an air-tight connexion. A further safeguard would be the inclusion of a more elastic pilot balloon than is at present supplied by the manufacturers. I join Dr. Rollason in considering that the shorter the tube beyond the cuff the better. The trachea is not of uniform length, and it is only too easy to intubate the right main bronchus.

In conclusion, may I emphasize that there is far more danger—i.e., inhalation of vomit—in not using a cuffed tube, where indicated, than in running the risk of these difficulties that have been described?—I am, etc.,

Twickenham, Middlesex. J. MIDDLETON PRICE.

SIR,—In spite of the knowledge that grease and oil cause deterioration of rubber, the use of greasy preparations to lubricate endotracheal tubes is widespread. Such lubrication increases the size of the tube and the thickness of its wall, due to absorption of the grease, and it also causes a weakening of the rubber. On plain tubes this has the disadvantage that the size of the tube ceases to correspond with its original gauge, and also the ratio of inside diameter to outside diameter falls, so that the airway becomes small in relation to the size of the tube. On cuffed tubes, however, the effects are far more serious. The cuffs lose their shape and, when inflated, become liable to distortion and may burst.

The following experiment was made to demonstrate the effects of a non-greasy lubricant on the cuffs of endotracheal tubes. The lubricants tested were 2% cinchocaina ("nupercaine") in "eucerin" (greasy) and 2% cinchocaina in a tragacanth paste (non-greasy). Three new pairs of similar cuffed endotracheal tubes were used. Pair 1 was lubricated with the tragacanth paste and pairs 2 and 3 with eucerin.

A daily regime representing normal use was designed. Each tube was lubricated and the cuff inflated with 15 ml. of air inside a 1-in. (2.5-cm.) test-tube. The tubes were then left for times vary-

ing between two and four hours, deflated, and washed in hot soapy water. Pairs 1 and 3 were then boiled for three minutes. Pair 2 was not boiled. It is customary in the theatres of St. Thomas's Hospital to sterilize tubes by boiling after use. This treatment was carried out for 14 days and the cuffs were inflated for a total of 50 hours. The illustration shows the condition of the cuffs at the end of this time. The wrinkling of the cuffs of the greased tubes (pairs 2 and 3) became apparent after two days' treatment. Pair 3, which was boiled as well as greased, showed a marked tendency to develop deformities of the cuffs when inflated on the last three days of the experiment. Pair 1, which was boiled but not greased, remained in a new condition throughout. This experiment, besides showing that grease rapidly produces deformity and weakness of the cuff, also shows that the effect of the grease is accelerated by boiling, though this in itself does not produce damage.

From time to time disasters or near disasters are reported which are attributed to obstruction of endotracheal tubes by distortion of the cuff during anaesthesia.[1 2] Dr. C. J. F. Baron's letter (*Journal*, August 16, p. 391) would seem to suggest that in order to prevent this the cuff should be placed away from the distal end of the tube. This has, however, the obvious drawback that if the distance between the proximal end of the cuff and the distal end of the tube exceeds the distance between the cords and the carina intubation of a bronchus will be performed.

The two main factors responsible for the production of dangerous deformities of the cuff are deterioration of the condition of the rubber of the cuff and excessive inflation of the cuff. The necessity for excessive inflation can be avoided by passing a tube which corresponds in size to the lumen of the trachea, so that the distension of the cuff necessary to produce an air-tight seal is minimal. The wrinkling of the cuffs resulting from the use of grease makes this difficult to achieve if damage to the larynx is to be avoided. If, however, no grease is used the cuff retains its close apposition to the wall of the tube, enabling a larger tube to be passed atraumatically. The rubber of the cuff is not unnecessarily weakened and will not develop aneurysmal deformities so easily.

The tragacanth paste used has been extensively tested in St. Thomas's Hospital for the past six months and has been found to be as effective a lubricant as the eucerin. Grease is never used now on cuffed endotracheal tubes, and as a result their useful life has been increased threefold.

I would like to thank the members of the Department of Anaesthetics at St. Thomas's Hospital who have helped in this investigation, and also Mr. Sultan Jouhar, of the Department of Medical Photography, for the illustration.—

I am, etc.,

London, S.E.1. R. W. Buckley.

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Theory of Cancer Treatment

Sir,—Dr. H. B. Hewitt (July 19, p. 158) thinks I have given "a very distorted picture of the cancer process" in my reflections on cancer treatment (June 14, p. 1301). This illuminating remark invites a comparison between the "true" and the "distorted" picture. In the elaborate picture presented by experimental cancer research we see the cancer cell, the conquering hero, in the foreground slaying normal cells, while in the background a wall of colossal dimensions is growing stone by stone. This is my impression after reading your annotation (July 12, p. 84). In my less elaborate picture John Cancer Cell is shown in all his misery, and closing in on him a living wall of leucocytes, lymphocytes, histioblasts, and fibroblasts. None of these two pictures gives a true likeness of the cancer process as a whole; each is telling half the story ("natural history"), illustrating one aspect, one phase, of the cancer process. Both are designed for different purposes, one for the use of those engaged in experimental research on how cancer is produced, the other for the guidance of those engaged in clinical research on how cancer is cured.

My contention is that the theory of treatment cannot be based on the theory of carcinogenesis; that the emancipation of clinical research from the patronage of experimental research is an urgent matter. The results of destructive treatment are not so convincing that the possibilities of conservative treatment ought to be left unexplored. According to the orthodox theory, a surgeon confronted with a case of late diagnosis in cancer only thinks of the cancer cells and their power to infiltrate and destroy normal tissues. Since he cannot reach them all, he may decide that the case is inoperable, tell his patient he can do nothing for him, and then go and dream of early diagnosis. But if he accepts my "distorted" picture of the cancer process, if he visualizes the microscopical healing processes going on in his patient, not only around the tumour but also around the lymphatics (described by Handley as "perilymphatic fibrosis"), his attitude may become quite different. He may have had his doubts before about the value of Halsted's "Theory of Inoculation"[1] which has ruled the teaching and technique of radical surgery for the last 60 years. Now he may think of revising the whole plan of surgical attack. The suggestions made by famous surgeons like Mayo, Delbet, Handley, Sauerbruch may enter his mind—that methods of conservative treatment ought to be evolved which make use of the spontaneous healing effects of the organism. He may wonder why these suggestions have never been followed up. I cannot see how clinical and pathological observations are "clearly refuted by experimental work on animal tumours." Experimental workers, with few exceptions, are determined to find the "full propensities of the disease" in the cancer cell or the virus and are therefore much too preoccupied with their strains and cultures to heed the stroma reaction of the host. But those who did, like W. Cramer or J. Mottram,[2] fully support my views. One can hardly refute Albert Fischer when he says he has found cells in the various parts of the body which resemble in every respect those which he found in tumours. The queer things which can be done to isolated cells under artificial conditions certainly have no bearing on the natural history of the disease. For the study of "aggressiveness" I refer to the description of a case of intravascular tumour generalization by Oertel.[3]

That tumour cells (or their extracts) have the faculty of stroma evocation, or induction, is characteristic for the genesis of tumours, which represents the first phase in their natural history; but we doctors are interested in the second phase, characterized by stroma reduction. Dr. Hewitt considers this phenomenon merely as a "coincidental side-effect" which "happens" to help the radiotherapist or "happens" to hinder the grafting of a tumour. He is a great believer in chance and evolution; he finds it reasonable to believe in the natural "helplessness" of the body against the aggressor, but not in its natural defences. I wonder how he interprets the fact that animal tumours show a remarkable tendency to spontaneous regression, so much so that in the opinion of leading cancer experts no safe conclusions can be drawn from therapeutical experiments on such animals. In man this tendency appears to be much less pronounced. Just because I believe—for once in agreement with Dr. Hewitt—that an "essential similarity of the biology of cancer in man and in animals" exists, I am satisfied that the weak stroma reaction in man can be brought to considerable heights and that here lies the field of new adventures in cancer surgery.

As a convincing example I chose our experience in radiotherapy. By no means did I wish to draw particular attention to this subject, which has been much more competently dealt with by Jolles and Koller.[4] If space had permitted I would have laid more stress on other, surgical, methods of stimulating the stroma reaction—for example, electrocautery. Here again it has been found that repeated, well-spaced sessions of superficial and partial cauterization give excellent results, local and systemic (Strauss),[5] while failures

were reported when the surgeon was too hasty and radical, burning too deep into the tissues. Repeated partial ligation is another method of effecting local reactions in tumours leading to regression (Allen).[6] Chemical irritants or infectious materials in small doses do the same, not because they kill all cancer cells, but because they set up an inflammation. As Grey Turner[7] said, discussing cancer of the colon : "It is significant that those cases in which the growth has been complicated by abscess formation often do extremely well."

I would be obliged if surgeons interested in the subject would send me notes about similar observations.—I am, etc.,

London, N.8. F. M. LEHMANN.

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Geographical Distribution of Cancer

SIR,—If my memory serves me right, a book was published in Paris by an author called Danichevsky, in the early part of the 'thirties, on the cause, distribution, and treatment of new growth in both man and plants, and I reviewed this book for the *British Journal of Radiology*.

The author believed that cancer was caused by cosmic radiation and that it was more prevalent in localities where the subsoil was of such a nature as to reflect a considerable amount of the cosmic radiation, while the incidence of cancer was low in localities where the subsoil absorbed most of the radiation. There were a number of graphs illustrating the relation between the nature of the subsoil and the incidence of cancer.—I am, etc.,

St. Peter Port, Guernsey. A. ORLEY.

Cancer and Organic Content of Soil

SIR,—Mr. C. D. Legon (September 27, p. 700) shows that in some areas in this country a high mortality from cancer is associated with a high content of organic matter in the soil as demonstrated by an ignition-loss test. In his comment he draws no distinction between organic matter in the form of peat and that due to heavy stocking. He implies that the dung of large flocks of hill sheep and large numbers of dairy cattle combine with the presence of mosses and fens to cause micronutrient deficiencies in food crops, and that these deficiencies are corrected in predominantly arable districts by the avoidance of excessive dunging.

Since the very existence of peat indicates a waterlogged, poorly oxygenated, and mineral deficient soil with a slow or altogether arrested humus turnover, on which the natural vegetation consists of highly specialized plant communities such as bog, moss, fen, and heath, it seems reasonable to postulate that food plants grown in such soil may be in some way deficient, quite apart from the effect of a high content of organic matter in the shape of peat or raw humus. The physicochemical and biological basis of plant life in such soil is probably quite different from that in well-drained, well-aerated soil in which the organic content is in the form of mild humus with a rapid turnover.

Dressing with dung, composting, ploughing in turf, and the other methods of raising the organic content of the soil, which is the aim of every good farmer, and has been for hundreds of years, are never likely to become excessive and to produce deficiencies in crops, since they give rise to a rapid turnover of humus on which healthy plant growth depends, and are the only sure methods of maintaining and increasing fertility. There is certainly no evidence that food produced in soil deficient in organic matter has a particularly benign effect on the people who eat it; McCarrison's work in India suggests quite the contrary.

Mr. Legon mentions that mosses and dairy cattle are possibly contributory towards crop deficiencies in Cheshire. The mosses are in the north of the county on the Lancashire border, and, where not built over, are largely under market-garden crops which supply the neighbouring industrial area and may well have some bearing on the problem, but the dairy farms are in the centre and south of the county, and most of the crops produced are for consumption on the farm; the principal crop for human consumption is wheat, which is no more likely to find its way into bread eaten in Cheshire than in any other county.

In view of the very clear distinction between the action on plant growth of peat or raw humus on the one hand and of mild humus on the other, I consider Mr. Legon's mention of dung in connexion with micronutrient deficiencies in food crops to be most misleading. He may, however, have sounded a timely warning of the possible dangers of reclaiming land for the growing of crops for which it is not suited.—I am, etc.,

Moreton-in-Marsh, Glos. E. H. EASON.

Refugees at Gaza

SIR,—I would like to present through the medium of your columns something of the seriousness of the immediate problem of the hospital care of Arab refugees in the Gaza strip. At the moment the C.M.S. Hospital at Gaza, which is largely responsible for the surgical care of the refugees in that area, is faced with urgent staffing problems; two surgeons are required immediately if the hospital is to continue the service which it has given to the refugees during the past five years.

A brief statement of the conditions obtaining in Gaza as they concern the work of the hospital will serve to indicate the magnitude and urgency of the problems which confront those responsible for its management. The total refugee population in the Gaza area is in the neighbourhood of 250,000, added to which are 50,000 or so permanent residents. The C.M.S. Hospital, an institution of 100 beds, is thus mainly responsible for the surgical care of a population of about 300,000 people. The beds are almost exclusively set aside for surgical cases, and the hospital functions as a surgical unit dealing with almost all the major surgery in the Gaza strip. It is well equipped and well staffed, with experienced nursing sisters and trained nurses. Enormous strains are put upon both staff and equipment, yet till now the job has been successfully coped with. The contracts of the two surgeons who are at the present time working in the hospital are due very shortly to expire, and they are for various reasons unable to offer for further periods. So far no successors have been found. If no one comes forward to fill the gap, the work will either cease completely or it will be seriously disorganized, with consequences which are unthinkable to anyone at all familiar with the medical aspect of the Arab refugee problem.

To any surgeons, or budding surgeons, who are not afraid of hard work, these posts offer not only a field for practical Christian service but also an unrivalled opportunity for gaining surgical experience. The attention of any interested readers (men or women) is directed to the further details of these posts in your advertisement columns (advertisement page 40). Particulars of the terms of service and allowances can be obtained from Dr. H. G. Anderson, Medical Superintendent, Church Missionary Society, London, E.C.4.

Any of the following doctors—P. E. J. Cutting (Ipswich), D. W. J. Radcliffe (Dover), and H. F. Lunn, who have served for varying periods at the Gaza Hospital, who are at present in England, and who can be contacted c/o Church Missionary Society, Salisbury Square, London, E.C.4—will be glad to provide detailed information of the nature of the work which is being done in the hospital and what would be required professionally from any intending candidate.—I am, etc.,

Old Cairo, Egypt. CHARLOTTE A. STUART.

Operative Method of Thrombosing Varicose Veins

SIR,—Mr. A. Johnston Abraham (August 2, p. 260) and Mr. F. D. Murphy (September 27, p. 725) describe "A New Operative Method of Causing Thrombosis in Varicose Veins." I really must point out that this treatment can hardly be called "new." In 1947 Santiago Triana Cortés and Arecio P. Rosas had been practising this method for some considerable time. To those who are interested the

technique is described in *Rev. Fac. Med. Bogota*, 1947, **15**, 629. The title of the article is, "The Surgical Therapy of Varices of the Lower Extremities by Inclusion of Foreign Bodies (Suture Threads) According to the Triana Cortés Technique."—I am, etc.,

London, W.1. R. Rowden Foote.

Harrow and Wealdstone Train Disaster

Sir,—As an old St. John Ambulance surgeon and having been in charge of the Wembley mobile unit during the blitz, I may be excused if I pass some observations on the rescue work in connexion with the terrible accident at Harrow and Wealdstone station.

The accident took place at 8.20 a.m. on a fine and dry day, and so conditions were fortunate for first aid. An outstanding episode was the arrival of the American Air Force medical unit at about 10.30 a.m., consisting of surgeons, orderlies, and nurses. They rendered most efficient first aid and also gave intravenous plasma transfusion on the spot. What was most important, every casualty went away properly labelled and marked to the awaiting ambulances. The local doctors did pioneer work. They climbed through the wreckage to the trapped victims, and large numbers of patients were given morphine injections, but once released they were whisked away so quickly that it was almost impossible to designate what treatment they had received. I endeavoured to give trapped victims drinks of bicarbonate of soda (two teaspoonfuls to the pint of water), but without exception those who were able to drink absolutely refused to take more than a feeding-cupful.

Naturally, enormous numbers of uniformed personnel were very soon on the spot—railwaymen, firemen, policemen, and, to begin with, a few Red Cross and St. John Ambulance men and officers. There was a sea of blue or dark blue uniforms, and it occurred to me that so far as medical personnel were concerned the blue and bluish uniforms should be discarded and a new uniform of a very distinctive colour introduced. Badges are not enough, although the white strap of the St. John men does stand out.

The purpose of this letter is to cast a few observations and to try to bring to the notice of the higher authorities some facts that emerge in an accident like this. There is no doubt that the Services should be able to supply a first-aid field unit like the American one, to proceed at short notice to anywhere in the country. In London, which is so well supplied with hospitals, this is not so important, but in country districts it could be really life-saving.—I am, etc.,

Wembley, Middlesex. R. Tudor-Edwards.

Sir,—While the terrible results of the Harrow and Wealdstone train crash are still fresh in all our minds, we would like to put forward some observations and suggestions arising from our experience in receiving the majority of the injured into the casualty department of this hospital. In doing so we would emphasize that we do not wish to detract in any way from the magnificent efforts of all concerned in the rescue operations, for whom we have the utmost admiration. Moreover, our observations are in no way original, being merely reminders of what many of us learnt in the war, and being well known to the medical branches of the Services.

Of the 96 patients arriving at this hospital during the morning of October 8, 54 were admitted to the wards. At least 13 of these had received injections of morphine before arrival, one patient receiving three injections and three others two injections each. In no case, however, was information available to us regarding the dosage and time given, and naturally many patients were doubtful whether they had received an injection or not. It is suggested, therefore, that doctors who may be called upon to give morphine in similar emergencies should carry with them a skin pencil or tie-on labels, and should enrol a lay volunteer to accompany them and record the necessary information in some such suitable way upon the patient. It is also pointed out that intravenous morphine (though admittedly not always practicable in such circumstances) is the quickest and most effective way of relieving pain in severe injuries, and obviates the necessity, and risks, of repeated intramuscular injections of the drug.

Secondly, we feel that hot sweet tea, and other and more stimulating fluids which were said to have been used, should be reserved for the lightly injured, the shaken, the frightened, and rescue workers, and withheld from the more seriously injured (whether or not intestinal trauma is suspected), who are likely to require general anaesthetics. These almost always vomit them sooner or later (often much later), and clearly do not assimilate them for many hours, thus complicating anaesthesia and further endangering the patient.

With regard to the use of transfusion fluids at the scene of such accidents, though it is difficult to do other than record impressions, we feel (and many with wartime experience will agree with us) that, in general, where surgical facilities are reasonably close at hand, the optimum time and place for transfusion are when the patient reaches the hospital where definitive treatment is to be carried out. On rare occasions, of course, transfusion on the spot may be life-saving, but more often the initial improvement produced is lost during the journey, and valuable time also, before a planned resuscitatory programme can be undertaken with transfusion as its mainstay and a patient fit for surgery as its object.

We fully realize that these few points are well known to most doctors and first-aid personnel, but they are apt, nevertheless, to be overlooked in times of crisis. Finally, it is perhaps worth noting that the burying of numbers of people in a tangled mass of wreckage such as was caused by this terrible accident produced on a small scale the circumstances and the types of injury we must learn to anticipate if aerial warfare should ever again overtake us.—We are, etc.,

Edgware General Hospital. Ian J. Gordon.
R. B. McGrigor.

POINTS FROM LETTERS

It's Overcoats

Dr. E. J. Dennison (East Grinstead) writes: In December, 1941, my unit set sail from a "cold"-ridden England, swathed in battledress and greatcoats. Within 10 days we thankfully changed into tropical kit and our virus-infested winter clothes were stowed away in kit-bags and trunks. Ten weeks' warm weather followed and it was the end of February when, after a 24-hour train journey due north from Basra, we arrived in Kirkuk. Here it was very cold indeed. Out came the battledress and greatcoats—and within 48 hours every other man in the unit had a typically English cold. We had not mixed with any other community on arrival, and the only possible explanation of such a sudden widespread infection was that we had brought it with us under the label "not wanted on voyage." The annual epidemic of autumn colds, which this year, at any rate in this area, seems worse than usual, prompts me to believe that the same factors possibly operate here. How many overcoats, thankfully relegated to their hooks in the spring, and heavily infested with viruses and "secondary invaders," have hung forgotten and uncleaned during the summer, to be hastily brought forth from cupboards under the stairs, perfunctorily shaken, perhaps brushed, and gratefully donned at the first spell of cold weather in the autumn.

Circumcision

Dr. W. R. Wilson (Doncaster) writes: In order to free the foreskin circumcision is by no means always needed, for in many cases it is held by adhesion of surfaces rather than by tightness of the opening. This is best dealt with by means of a small pair of Spencer Wells forceps of the "mosquito" type with curved end. They are usually quite easy to insert and can then be opened and moved about in all directions to the full limit of the space. In spite of what has been said about there not being any anatomical differentiation between the layers in the first two or three years, I personally have never found any material resistance, nor bleeding, nor unhealthy reaction afterwards. This makes me wonder what foundation there can be for the assertion. However this may be, retraction is almost invariably quite easy by now. If not, and subsequent stretchings of the opening fail, circumcision is plainly indicated.

Obituary

P. H. MITCHINER, C.B., C.B.E., M.D., M.S., F.R.C.S.

The death of Mr. Philip Mitchiner at the age of 64, which took place in London on October 15, removes a man of high distinction in the fields of surgery, of academic life, and of military medicine. He will be sorely missed in a number of council chambers and in many other places, not least at St. Thomas's Hospital, to which he gave close upon a quarter of a century of service, and at the Royal College of Surgeons, where he was Hunterian professor as long ago as 1923, and of which he had been for the last two years a vice-president and for many years a member of the Court of Examiners. He was a man of soldierly bearing and accustomed to command, but behind the military front were many very human qualities, including a keen sense of humour, and those who came into closer touch with him soon mingled their respect with affection.

[*Elliott & Fry, London*

Philip Henry Mitchiner was born at Croydon on June 17, 1888, and attended the Reigate Grammar School. From there he entered St. Thomas's Hospital, where he showed unusual brilliance as a student, winning various scholarships on his way. He qualified M.B., B.S., London, with gold medal, in 1912, and, selecting surgery as his special field, took the Fellowship of the Royal College of Surgeons in the following year, and became Master of Surgery the year after that. He held certain residential posts at St. Thomas's, and with the coming of the first world war found himself registrar at the Fifth London General Hospital. That was far too unadventurous for young Mitchiner, and soon he was serving with the Serbian army at Salonika. For his work in that field he was mentioned in dispatches, received the knighthood of St. Sava and the gold medal for devoted service, and from Russia the Order of St. Stanislaus. The end of the war did not terminate his association with Serbia, now part of Yugoslavia, and in 1920–1 he returned to that area as surgeon to the Serbian Relief Fund under the Serbian Government.

Settling again in London in 1922, Mitchiner became surgeon to out-patients at the Royal Northern Hospital, a post he retained until 1926. Soon the opportunity came for appointment on the staff of his old hospital, St. Thomas's, as assistant surgeon; he became full surgeon in 1935, and on his retirement three years ago consulting surgeon, a post which he held at the time of his death. His part in the second world war, although he was over 50 at its outbreak, was as adventurous as in the first. Much of his time was spent as D.D.M.S. at Corps headquarters of the Air Defence of Britain at Stanmore, but in 1940 he was D.D.M.S. of IV Corps in Norway, and later of V Corps. He returned to his anti-aircraft command in 1941, and in 1942 he was appointed major-general and D.D.M.S., Northern Command. In 1944 until the end of the war he held an appointment as consulting surgeon to the Middle East Forces, where he served as administrative medical officer under Montgomery, Auchinleck, and other great commanders. Early in the war he had found time to produce two manuals, one on the *Modern Treatment of Burns and Scalds* and the other, jointly with Sir Ernest Cowell, on *Medical Organization and Surgical Practice in Air Raids*. These were not his only essays in medical literature, for he was co-author, with Mr. W. H. C. Romanis, of two textbooks which have run through many editions, *Science and Practice of Surgery* and *Surgical Emergencies in Practice*.

Military medicine, and indeed military life in general, were Mitchiner's great love. He began his military career when he was only 16 years of age, as a cadet in the Queen's Volunteers, and he was one of the earliest recruits to the University Officers Training Corps in London when it was formed a few years later. As a medical student he took his first parade in a snowstorm at Millbank in January, 1908. Presently he became sergeant, and the young officer under whom he served was the future Lord Webb-Johnson, under whose presidency in the council of the Royal College of Surgeons he was one day to sit. For many years Mitchiner was officer in charge of the London University Officers Training Corps, and indeed, in a popular reference book, this, with the Territorial Association, is listed as his only recreation. One of the great pleasures in his busy life was to bring cadets to Millbank and initiate them in the routine of barracks, even down to such details as the drawing of pay and rations, the laying out of kit, and the significance of the various bugle calls. Between the wars he worked enthusiastically in the Army Medical Service, and from 1933 to 1935 was A.D.M.S. of the Second London Anti-Aircraft Division, and afterwards of the First. Another interest of his was the Casualties Union, of which he was president—a voluntary body of trained "casualties" to help teachers of first-aid by simulating accidents and acting as realistic casualties.

Along with all this life of action, however, he was a man of acute mind, and his interventions in the several councils and committees on which he served were always very much to the point. In 1951 he was appointed deputy Vice-Chancellor of the University of London, an appointment renewed in the following year. He was also adviser to the Postgraduate Medical Education Committee of the South-west Metropolian Region, a member of the administrative committee of the War Memorial Fund of the Army Medical Services, and recently, representing his College, he had been made a member of the Council of the Royal College of Veterinary Surgeons.

In 1932 he became honorary surgeon to the King. He was made Commander of the Order of the British Empire in 1938, and of the Order of the Bath in 1944. He is survived by his wife, whom he married in 1928.

We are indebed to Sir Max Page for the following appreciation: Philip Mitchiner, by both his writing and his clinical work, established himself as one of that diminishing breed—the general surgeon. His death, at a relatively early age, is a severe loss to the profession, for he was possessed of a robust critical spirit which found expression on many committees, and there often proved a vitalizing factor. A certain brusqueness or occasional unorthodoxy of speech seldom hurt the sensitive, its effect being always mitigated by his transparent honesty of purpose and by the sound horse sense which usually characterized his pronouncements. At St. Thomas's Hospital he was a most popular and successful teacher of undergraduates. In his latter years he did a great deal of examining for various qualifying authorities, and

was reputed to expect a high standard of clear thinking from the candidate, yet to be possessed of sympathy and understanding for the tongue-tied.

He had a strong sense of public duty, and his services to the Royal College of Surgeons and to London University are outstanding examples of this trend. He was a loyal and hard-working member of any organization with which he became associated; his long attachment to the medical Territorial unit of London University was an outstanding example of this side of his character. In the first world war love of enterprise and adventure found a congenial outlet in his service with the Serbian Army. In the last war his experience and rank in the Territorial Army led to his employment on the administrative side until towards the end, when he served as a consultant in the Middle East Command.

On the Council of the College of Surgeons he will be much missed, for he provided a useful link with London University and his occasional trenchant criticism and unfailing common sense at the council board carried great weight. He was an admirable secretary to a College club, both for his managing ability and for the vein of dry wit which illuminated his minutes. Always a willing horse, in the last few years he had had several bouts of ill-health. His spirit was never better shown than by an entire absence of self-pity in relation to these, and by the resilience and determination with which he got back into harness. He was happily married to a most popular sister of St. Thomas's, to whom much sympathy is extended in her early widowhood.

We are indebted to Sir Ernest Cowell for the following appreciation: In the passing of Philip Mitchiner, not only the Territorial Army but the medical services of the Regular Army have lost a brilliant, wise, and forceful leader. Philip Mitchiner and I had been fellow part-time soldiers ever since the early days of the University of London Officers' Training Corps, when in 1910 we attended the first camp together. We enjoyed the valuable experience of learning to live under active service conditions, sleeping eight in a tent in wet weather. As N.C.O.s we learned the details of internal administration and enjoyed the privileges of the sergeants' mess. In the 1914–18 war Mitchiner volunteered for service with the Serbian Army, where he did good work and was suitably decorated. He served in many theatres, notably in Salonika, being engaged mostly in administrative and staff duties. In the interval between wars he served in the University of London O.T.C., commanding the unit for a number of years and always finding time for soldiering in spite of extensive hospital commitments and increasing private practice. In 1938 we co-operated in producing a manual of practice for what we both felt to be the impending war: the book, *Medical Organization and Surgical Practice in Air Raids*, was well received and I believe was helpful to many engaged in organizing civil defence and operating as war surgeons.

The last war found Mitchiner still serving, and when V Corps was formed he was appointed D.D.M.S.; this carried the rank of brigadier. All the staff officers of Corps Headquarters were expected to be physically fit and were required to do long-distance runs at least twice a week. At about this time cardiac symptoms began to appear and he was advised to take things easily. In the ill-fated expedition to Norway Mitchiner was the D.D.M.S. and passed through an anxious time. He told me one day how he was going along a road when there was considerable shelling. He added: "My doctors had told me not to hurry, and so I acquired a great reputation for bravery." On his return from Norway he was appointed D.D.M.S. Anti-Aircraft Command, where he established and administered an extensive and difficult medical service. In 1942 he was promoted to the rank of major-general, thus being the first T.A. officer to hold such high rank in the second world war and following Major-General Sir Richard Luce of the first world war. In 1943 Mitchiner was posted as D.D.M.S. Northern Command, again making history for the T.A.: no Territorial medical officer had ever occupied this post before—always regarded as one of the plums of the Service. On leaving Northern Command he carried out the duties of consulting surgeon in the Middle East. Up to the time of his death he was acting as adviser on T.A. matters to the Director-General of Army Medical Services.

Mitchiner's interest in the R.A.M.C. remained to the end, in spite of increasing demands entailed by such offices as the Vice-President of the Royal College of Surgeons. He attended the annual T.A. Challenge Shield Competition in September and was present at the meeting of the Auxiliary R.A.M.C. Funds Committee on October 6. Philip Mitchiner's name will long be honoured by hundreds of officers and other ranks of the R.A.M.C.(T.A.). His facile pen and ready wit, his self-sacrificing enthusiasm, and his wise counsel provided a rare combination of qualities. I would like to express the sympathy of all his friends to his widow, whose devoted care contributed so much to his success in life.

W. E. GYE, M.D., F.R.C.P., F.R.S.

Dr. W. E. Gye, director of the Imperial Cancer Research Fund from 1936 to 1949, died in Perth, Western Australia, on October 14, aged 68 years.

William Ewart Bullock—who later changed his surname to Gye, the maiden name of his first wife—was born on August 11, 1884, at the small Derbyshire village of Breaston. His father was a signalman on the Midland Railway, who, like many another, found difficulty in keeping a largish family adequately clothed and fed. The economic struggle must have been particularly severe at times, for Gye once mentioned his vivid memory of the sense of dire calamity which in his early childhood hung over the household for some days following his accidental loss of a single sixpenny-piece from his mother's housekeeping money. His schooling was local, and at the end of it he had to begin earning a living. He tried several of the available occupations without finding one likely to prove lastingly satisfactory, and he then became a "pupil teacher" and fortunately came under the tutorial care and personal influence of Samuel Clegg, who had exceptionally strong enthusiasms for the literary and artistic side of human activities. Gye's lasting love of poetry and his keen appreciation of literary style had its real beginnings in these days.

[Bassano, London

His training period over, Gye gave up teaching to become a clerk on the Midland Railway. He was able to continue his study of science, and on the advice of Mr. Clegg he sat an examination for a scholarship tenable at University College, Nottingham, and was successful. His progress was unusually rapid, and in due course he gained his London B.Sc. in chemistry. In his student days also Gye had become a good cricketer, probably up to county standard, and in later years he greatly enjoyed watching test matches and other important games. At Nottingham Gye became very friendly with D. H. Lawrence, at that time a fellow student: they seemed to have found much of interest in one another.

After taking his degree Gye spent a year in Birmingham teaching, and then in 1909 he accepted the offer of

a friend—a second friend seems also to have helped to some extent later—of funds to enable him to study medicine. The offer was intended as a gift, but Gye lived cheaply and later insisted in regarding the money as a loan, and paid it back in full. After an unusually brilliant course in Edinburgh Gye graduated M.B., Ch.B. in 1912, coming out top in the final examination, and then after a month or two as an assistant in general practice he returned to the university, and in 1913 proceeded M.D. with the award of a Gold Medal. He then joined the staff of the Imperial Cancer Research Fund, at that time in Queen Square, London. Here he met as colleagues Bashford, Murray, and Russell, and became expert in the histological interpretation of cancer sections. This period was important in his life in that it laid the foundations for the work to which he was to dedicate himself a few years later. When the first world war broke out Gye joined the R.A.M.C. and served in France and then in Italy in charge of a field ambulance.

He returned to London on demobilization and joined the scientific staff of the National Institute for Medical Research, Hampstead, then coming into being. After making some original and important observations on "defence rupture" in anaerobic infections in collaboration with W. Cramer, Gye became interested in silicosis. He collaborated with E. H. Kettle in investigations of silicosis and miners' phthisis. Gye appears to have had a hand in the initiation of the dog-distemper investigations conducted by the Medical Research Council. However, since the experimental work on this virus disease had to wait until a colony of distemper-free dogs was established, Gye occupied himself in preliminary studies of another filterable virus. He obtained the Rous fowl sarcoma and was so deeply immersed in the fowl tumour problem when active work on distemper virus was ready to proceed that arrangements were made to permit him to proceed with the tumour work.

Gye continued his investigations of fowl tumours, and in 1925 aroused much controversy by the publication of a paper in which he claimed that not only fowl tumours but other cancers were due to viruses which could be cultivated in cell-free media and photographed by ultra-violet photomicrography. Much further work was carried out in collaboration with W. J. Purdy, and in 1931 Gye and Purdy presented their work on fowl tumours in detail in a book *The Cause of Cancer*. The central idea in the thesis presented in this work is that the specificity of various growths is determined by a "specific host" factor, not by the properties of the virus.

There were differences of opinion about some of Gye's work and the validity of his conclusions, but he continued to make valuable, if controversial, contributions to cancer research. To-day it seems generally conceded that his chief contribution in the early period was that he did not allow the filterable fowl tumours to be set aside as unique conditions of no significance to the cancer problem. He continued to keep the virus hypothesis an active issue. In the same issue of this *Journal* (March 26, 1949), in which was printed a lecture he delivered at the Royal College of Surgeons entitled "The Propagation of Mouse Tumours by Means of Dried Tissue," we published a leading article in which his latest work was discussed. The following quotation is relevant:

> The core of the whole argument is this: are the filterable tumours things apart, or are they essentially the same as other tumours, differing only in some quantitative manner, so that our techniques just fail (as they sometimes fail even with fowl tumours) to reveal a continuing cause, separable from the living cell?

Gye concluded in his lecture that certain mouse sarcomata had such a continuing cause and that it was probably viral in nature. This conclusion did not find general acceptance, but has stimulated research in this country and abroad which has yielded much additional information on the ability of tumour cells to withstand prolonged freezing or dehydration.

In 1936 Gye became director of the Imperial Cancer Research Fund, and he took a full advisory share in the designing and building of the new laboratories at Mill Hill. In 1938 he was elected F.R.S., and in 1947 he was appointed Professor of Experimental Pathology at the Royal College of Surgeons. He retired in 1949, having been in failing health for some time.

Gye was twice married. In 1913 he married Miss Elsa Gye, who died in 1943. In 1948 he married Professor Ida Mann, and a year later he went with her to Western Australia. His health continued poor until his death. Our sympathies are offered to Professor Ida Mann and the three sons of the first marriage, all of whom survive him.

We are indebted to Dr. W. J. Purdy for the following appreciation: Among the leaders in pathology, especially in experimental pathology, in this country, in the period immediately following the first world war, was a notable group of men closely held together by personal contacts and friendships arising from a particular type of scientific outlook and preoccupation. Among these workers were those who founded the *British Journal of Experimental Pathology*, and most, or all, were influential members of the Medical Research Club. To-day only a very few of this once familiar group are left. Kettle, MacIntosh, Murray, Bullock, Topley, Almroth Wright, and others are gone. Now Gye is gone, and with his death there is a vivid sense of loss.

When Gye started his cancer investigations research workers had apparently reached a complete but triumphal impasse in their search for the cancer cause. There was a universal agreement that cancer qualities certainly depended on some subtle feature in which cancerous cells differed from normal cells—some mutation, for instance—and must therefore involve "life processes" themselves, intimate knowledge of which must for ever remain beyond our reach. That was the situation about 1914, and with the conclusion Gye, at that time, agreed, but at the same time he saw how completely this conclusion was responsible for the existing lack of drive and initiative being displayed by cancer research workers in this aspect of their work.

Presently, however, and particularly during his period of war service, Gye pondered much over the likely significance of the filterable fowl cancers which Rous had recently discovered and investigated, but which already were being so readily and conveniently dismissed and ignored as spurious. To Gye it seemed that here was a cancer agent conveniently exposed to investigation, and after he had joined the staff of the M.R.C., and in face of much well-informed opposition, he determined on an attempt to follow up the work of Rous from the point at which Rous had abandoned it. After a time Gye discovered that the essential active agent in a Rous filtrate contains two significant factors. One of these, he showed, is a product of the cancerous cell itself, and the bearer of that remarkable cell specificity which is exhibited by filtrates and differs strictly according to the kind of cancer from which it is derived. The other factor, Gye showed, has all the qualities of a parasitic virus, but does not differ with the kind of tumour from which it is derived, being of only one variety or perhaps very few varieties. It seems to me that the factor which is the product of the cell must be considered Gye's key discovery. What part it plays in the economy of the cancer cell he did not know, but its recognition enabled him to investigate the accompanying virus. Gye conceived of the virus as stimu-

lating its host-cell to malignant activities and to be the true cause of cancer growth in a medical sense. Thus Gye's findings showed that the theoretical arguments on which the prevalent views had been based were invalid, and that no real impasse had been reached at all. As a further consequence of his work welcome conflict, enthusiasm, and vitality returned to cancer research.

Perhaps Gye's outstanding qualities were his absolute scientific honesty, his treatment of junior colleagues as friends in so far as they wished it, his willingness to fight with superiors over what he thought should be done; his efforts to give his qualified and technical assistants justice and friendship and ready help from his vast store of knowledge; his courage and self-reliance in face of opposition in scientific judgments; his loyalty to superiors; and his habit of attacking theories and conclusions with vigour, but never the holders of those opinions. The publicity given to him and his work in the public press was certainly not of his contriving: indeed, on various grounds he much regretted it, right from the beginning. Curiosity was the force that drove him most strongly. Once Captain S. R. Douglas, his departmental chief at the time, warningly remarked that someone else was working on similar lines and might publish first. Gye's reply was, "Well, what does that matter? If he does I shall then have my answer and can pass on without further work"—a remark typical of the man, and without any trace of jealousy.

A. E. GOW, M.D., F.R.C.P.

We are indebted to Dr. M. H. Gordon for the following appreciation of the late Dr. A. E. Gow, whose death was recorded in the *Journal* of October 4 (p. 781):

Dr. A. E. Gow had personal qualities that endeared him to all who knew him. He was one of that rare class—a highly skilled clinical pathologist who ultimately became senior physician to his hospital. When the new pathological building at St. Bartholomew's was opened in 1909 under Sir Frederick Andrewes, Gow was one of the junior demonstrators, and as he had recently been house-physician to Dr. (now Lord) Horder at the Great Northern Hospital he was always an adept at blood culture, blood counting, and all the increasing applications of bacteriology and serology in the service of clinical diagnosis. In 1932, when the report of the combined effort to define the causal agent of Hodgkin's disease—known as the Rose Research—was published, a stage had been reached when all other pathogenic organisms had been excluded, excepting the elementary bodies, or E.B.s, similar in appearance to those present in vaccinia and smallpox and known to be bodies of the actual virus. In order to test the significance of these "Hodgkin bodies" it was necessary to try the effect of a heated suspension or vaccine of them on a case of Hodgkin's disease. Gow carried this out with great care and skill, with the result that convincing evidence was found of the existence of a specific hypersensitivity to these E.B.s in patients affected by Hodgkin's disease (see *Proc. roy. Soc. Med.*, 1934, 27, 1035). This was a great step forward, and prepared the way for the next stage when Dr. E. C. Warner showed that this specific allergy to the Hodgkin E.B.s could be overcome by combining them with their specific antibodies before injection.

Dr. Robert Elrick Marwick, who died in Edinburgh on August 9, was born in Kirkcaldy in 1881, and was educated in Edinburgh, where he graduated M.B., Ch.B. at the university in 1906. He practised at Cockburnspath, Berwickshire, for a short time, and then in London, after which he joined, and later succeeded, Dr. McLachlan at Longtown, Cumberland. His work was interrupted by the first world war, during which he served in France in the R.A.M.C. Later he returned to Longtown, and afterwards was in practice at Liberton, Edinburgh. From 1943 until the end of July, 1952, he held an appointment in the Edinburgh office of the Ministry of Pensions. Dr. Marwick was one of the first doctors to arrive at the scene of the great troop-train disaster at Gretna in May, 1915, and he did valuable first-aid work. His personality was a stimulant to his patients and to all who came in contact with him. He is survived by his wife and one married daughter.—R. W. B.

Medical Notes in Parliament

EXPERIMENTS ON ANIMALS

Lord Dowding opened a debate in the House of Lords on October 14 by drawing attention to the unnecessary suffering caused to animals by medical and surgical experiments. He said that even if it could be proved that human beings benefited from the suffering of animals its infliction could be unethical and wrong. There was neither adequate inspection under the 1876 Act on cruelty to animals, nor proper enforcement. The number of experiments was grossly excessive, and they were unduly repetitive. Most of the experiments were impractical when it came to applying them to human maladies, and they might be definitely injurious. He claimed that the volume of criticism from doctors and medical journals was steadily growing, and he demanded an inquiry into the conditions which had arisen since the last Royal Commission reported in 1912, particularly the new field of animal exploitation in the manufacture and testing of drugs.

Lord Webb-Johnson spoke of his experience when President of the Royal College of Surgeons. He said he had refused to sign many applications for such experiments, either because the experimenter was not working under satisfactory conditions, or because the experiment had been repeated a sufficient number of times to prove the results.

More precautions were taken in this country than anywhere else in the world. The suggestion that experimental workers were indifferent to the suffering of the animals was far from the truth.

Dramatic facts had been brought to light by such experiments. One was the placing of an artificial valve in the aorta, which had proved that an incompetent aortic valve could be replaced by a plastic valve. He had seen a dog which had been so operated on eight months before being raced round the track belonging to the laboratories. The only difference he could see from a normal dog was that instead of the normal beat there was the click of the artificial valve. These things were worth doing, and human lives were saved by them.

Adequate Precautions

For the Government, the Earl of Selkirk, Lord-in-Waiting, said the number of experiments had considerably increased, but almost all consisted in inoculations, applications of substances, or the administration of a drug. He described the system of inspection, the reports to the chief inspector, and the annual report to Parliament, and said the chief inspector assured him that he knew what was going on in every place on his register. It was true there had been no prosecutions under the 1876 Act, but that was not a satisfactory way of judging its operation. Certificates and licences had been refused, warnings had been issued, and in some cases matters had been brought to the notice of heads of departments, or senior officers of the universities. After careful investigation in 1948 the then Home Secretary had decided there was no need for a new Royal Commission, and nothing had arisen recently to cause the present Home Secretary to alter that decision.

Lord Dowding withdrew his motion.

Road Accidents

In the House of Lords on October 15 Lord Hampton called attention to the continuing tragedy of road accidents. He said that the statistics of road casualties did not show a great improvement during the post-war years. In 1938 the population exposed to risk was 46,208,000. This

rose in 1951 to nearly 49,000,000. In 1938 the number of vehicles licensed was 3,052,000, which rose to 4,296,000 in 1951. During the same period the quantity of motor fuel consumed rose by 27%. The toll of the road was indeed heavy. All road users should be grateful for the efforts to secure their safety.

Lord Lucas of Chilworth said that until the Government treated this matter seriously and until the public conscience demanded action from the Government the House should go on debating it. The death roll in the railway tragedy at Harrow only equalled one week's toll on the roads. The loss of life at Lynmouth only equalled two days' toll on the roads. Last year 5,250 people were killed on the roads and 52,369 were seriously injured. Yet he believed that the question of road accidents had never been thought of sufficient importance to appear on a Cabinet agenda. Over 80% of the accidents happened in built-up areas. Congestion, not speed, was the greatest factor in accidents in such areas.

Lord Llewellin said he did not think the Government could solve the problem. In the last 50 years there have been 7,000,000 road casualties in accidents involving injury or death. The deaths per million of the population in 1935 were 143, in 1938 were 144, and last year went down to 107. The number of children killed per million of population were 27 in 1935, 24 in 1938, and 19 in 1951. The main danger area was from the age of 5 or 6 up to 15. When he got above 55 the citizen passed into another vulnerable area. The percentage of population over that age was now 21% compared with 17% 20 years ago. Because of additional births just after the war there were at present 1,000,000 extra children under 15 years of age and a large number in the vital 5 to 6 years age group where the most accidents occurred.

Menace of Alcohol

Lord Strabolgi said that drinking by many motorists was a fruitful cause of accidents. The Saturday night period was the most dangerous of all. A special study of motor vehicle accidents in the United States during 1942 showed that in one out of every five deaths the driver or the pedestrian had been drinking and that one out of every nine drivers and one out of every six pedestrians involved in fatal accidents had been drinking. When new legislation to control road traffic is introduced he hoped it would be made an offence to drink at all during or before a motor-car journey. The number of fatal accidents in Sweden had declined sharply since a law was introduced making it a criminal offence for the driver of a motor vehicle to take any alcohol at all.

Lord Leathers, replying for the Government, said the debate had been most helpful. Altogether £3,000,000 would be spent this year and next in improving the black spots on the roads. A wide range of propaganda and publicity was being continued to bring home to all their individual responsibility on the roads. Whereas in 1938 deaths on the roads numbered 6,648 the number last year was down to 5,250, a reduction of over 20%, although the population had risen by over 3,000,000 and the number of road vehicles had increased by 50%. He would study the remarks which had been made about drink as it affected safety on the roads. Some people showed the effects of a small amount of drink quickly and acutely. There was no easy footrule by which to measure the effect of alcohol in this connexion.

Lord Hampton, in an addendum to his own speech, said that road casualties in 1951 were reduced by 7% as compared with 1938, while deaths were down by 21%.

Criminal Responsibility.—The Home Secretary will not recommend the appointment of a Royal Commission to consider changes in the law relating to the criminal responsibility of persons of unsound mind. The Royal Commission on Capital Punishment, appointed in 1949, had been examining these problems and would doubtless include observations on them in its report, which should be available within the next few months.

Shortage of Dentists.—Asked how far the number of dentists at present available falls short of requirements to provide a satisfactory dental service, Mr. Macleod replied that on the estimates made by the Teviot Committee the shortage may be of the order of 9,000.

Attested Cattle.—Of the cattle in Great Britain 37% are attested.

Experiments on Animals.—The total number of experiments performed in 1951 on living animals was 1,919,424. Of these, 1,665,120 experiments not involving any procedure more severe than simple inoculation or superficial venesection were performed without anaesthetics. Cats, dogs, horses, asses, or mules were used in 10,262 experiments.

Atomic Burns.—No paste is available to protect the face and eyes from flash burns from atomic explosion, but simple methods of screening the faces and hands of those who may have to be out of doors are under investigation.

The Services

The name of Acting Interim Surgeon Lieutenant-Commander J. S. Ritchie, R.N., H.M.S. *Morecambe Bay*, appears in a list of those mentioned in dispatches for distinguished service in operations in Korean waters.

The name of Colonel G. Anderton, O.B.E., late R.A.M.C., appears in a list of those who have been mentioned in dispatches in recognition of gallant and distinguished services in Korea during the period January 1 to June 30, 1952.

Captain R. Barnes, R.A.A.M.C., has been appointed M.B.E. (Military Division) in recognition of gallant and distinguished services in Korea.

Vital Statistics

Unusual Outbreak at Bath

For the following account of an outbreak of infectious disease at Bath we are indebted to Dr. H. Campbell, Superintendent of Bath Isolation Hospital, and Dr. L. F. McWilliams, Deputy Medical Officer of Health, Bath County Borough.

Since September 10 there have been admitted from the administrative area of the Bath County Borough to the Isolation Hospital 17 cases in which clinical examination and cerebrospinal-fluid investigation suggested a diagnosis of poliomyelitis (non-paralytic). (Ten additional cases from the Bath Clinical Area during the same period showed the classical symptoms and signs of poliomyelitis; all showed a pleocytosis and increased protein content of the C.S.F. and associated weakness or paresis of one or more groups of muscles.)

The first case in the city outbreak was a man aged 33 years. For two days before admission there had been slight diarrhoea, and then intense frontal headache, severe photophobia, and vomiting occurred. Temperature was 101° F. (38.3° C.) on admission. No abnormal clinical signs were elicited apart from some neck stiffness. Lumbar puncture showed the C.S.F. under raised pressure. Cell count was normal, but the protein was 60 mg. per 100 ml. Headache and photophobia persisted for two days, and thereafter he made a rapid recovery without complications.

His son was admitted two days later with a similar illness, although the headache and photophobia were less severe. The C.S.F. showed slight lymphocytic pleocytosis and raised protein content. Another contact, a man aged 19 years, was admitted three days after the boy, with headache, photophobia, and vomiting. The C.S.F. findings were a definite lymphocytic pleocytosis and raised protein. Further cases with essentially the same clinical picture, the same C.S.F. findings, and the same rapid recovery occurred. Stools and sera have been sent to the Virus Laboratory and results are awaited.

The early cases came from three family groups who had all been in contact with one another and lived in the same area of the city. On investigating the home contacts in these cases, it came to light that most other members of the households involved had recently suffered from headache and vomiting to a lesser degree. Moreover, several other

families in adjacent homes were likewise affected, but their illness had been transitory and had not required calling in their doctor.

Absences of children from four schools during the last three weeks in September in the affected area were checked by home visits. So far as it was possible to ascertain, about ninety children and adults were traced with recent histories of headache, vomiting, and diarrhoea—short in duration but sufficient to incapacitate for a few days. There was no rodent infestation of the area, and in addition the moderate lymphocytic pleocytosis ruled out a choriomeningitis outbreak. Although the hospital admissions have been labelled poliomyelitis (non-paralytic), the extent of the disease in the community and the clinical picture appear to suggest a Coxsackie virus infection.

In a paper delivered at the International Poliomyelitis Conference on September 4, 1951, at Copenhagen, Professor Curnen, of Yale University School of Medicine, described[1] an illness resembling non-paralytic poliomyelitis occurring during 1948 in Connecticut and Rhode Island. Coxsackie virus was recovered from faeces in some cases, and neutralizing antibodies were demonstrated in the serum of affected persons. Cerebrospinal fluid showed a moderate pleocytosis. The course of the illness described by him was relatively brief, uncomplicated, and ended in complete recovery. In individual patients differentiation from non-paralytic poliomyelitis on the basis of clinical findings did not appear to be possible.

Quarterly Returns for Eire

The birth rate during the second quarter of 1952 was 23.8 per 1,000, being 1.3 above the rate for the same quarter of 1951. The infant mortality rate was 35 per 1,000 registered births; this rate was 11 below that of the corresponding quarter of 1951, and was the lowest rate ever recorded for any quarter. The general death rate was 11.8 per 1,000, being 1.8 below the rate for the preceding June quarter. 178 deaths were attributed to the principal epidemic diseases; these included 73 from influenza, 43 from gastro-enteritis under 2 years, 27 from measles, and 24 from whooping-cough. Deaths from respiratory tuberculosis numbered 362 and from other forms of tuberculosis 88; these were 109 and 51 fewer, respectively, than the totals for the second quarter of 1951.

Infectious Diseases

Rises were recorded in the number of notifications of measles 1,424, scarlet fever 120, and dysentery 69 in England and Wales during the week ending October 4, while the only large fall was whooping-cough 132.

An increase in the incidence of measles was reported throughout the country. The largest rises were London 200, Yorkshire West Riding 165, Glamorganshire 156, and Essex 107. A small rise in the incidence of scarlet fever occurred in every region with the exceptions of London and the south-east region. The number of notifications of diphtheria was 10 more than in the preceding week, mainly owing to a rise of 8 in Lancashire. Only small variations were recorded in the local trends of whooping-cough.

Notifications of paratyphoid fever numbered 8 fewer than in the preceding week, mainly because of a decline of 7 in Wales. The largest return was Glamorganshire with 7 cases.

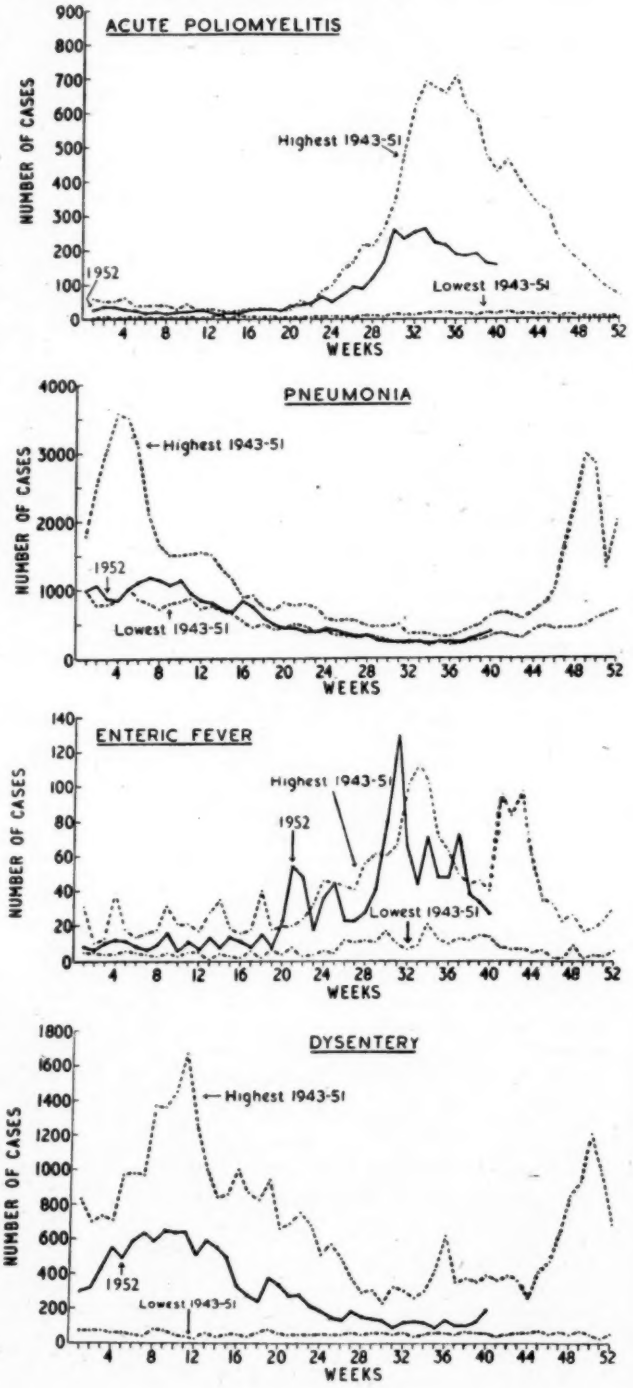
The number of notifications of acute poliomyelitis was 3 less than in the preceding week for both paralytic and non-paralytic cases. The largest returns were London 22 (Hampstead 4), an increase of 13 on the preceding week; Essex 17 (Southend-on-Sea C.B. 11); and Yorkshire West Riding 14.

The largest returns of dysentery were Lancashire 35 (Blackburn R.D. 20), London 28 (Finsbury 11), Wiltshire 24 (Calne and Chippenham R.D. 24), Durham 20 (Stockton-on-Tees M.B. 10), Yorkshire West Riding 17, and Middlesex 10. In Scotland the notifications in Glasgow rose from 48 to 90.

[1] *British Medical Journal*, September 22, 1951, p. 732.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1943–51 are shown thus - - - - -, the figures for 1952 thus ————. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



Week Ending October 11

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,617, whooping-cough 1,078, diphtheria 24, measles 5,716, acute poliomyelitis 109, dysentery 160, paratyphoid fever 25, and typhoid fever 2.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 4** (No. 40) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	25	1	13	2	1	30	1	16	0	2
Dysentery	192	28	117	1	1	124	33	62	1	
Encephalitis, acute	1	0	0	0		15	0	0	0	
Enteric fever:										
Typhoid	4	0	3	2	1	9	0	0	0	0
Paratyphoid	23	2	0	0		31	0	2 (B)	2	
Food-poisoning	117	15		23		125	16		2	
Infective enteritis or diarrhoea under 2 years				15	29				10	55
Measles*	4,696	554	74	32	33	1,466	22	82	137	114
Meningococcal infection	29	4	9	0		27	4	13	1	1
Ophthalmia neonatorum	32	2	13	0		45	1	9	0	
Pneumonia †	371	22	213	6		310	18	135	1	1
Poliomyelitis, acute:										
Paralytic	101	15	3	9	7	56	1	15	2	4
Non-paralytic	54	7				40	4			
Puerperal fever§	219	33	15	0	1	241	31	18	0	
Scarlet fever	1,284	118	275	13	58	869	66	214	30	33
Tuberculosis:										
Respiratory			120	33				136	43	
Non-respiratory			17	4				26	5	
Whooping-cough	1,126	86	69	17	35	1,589	62	315	25	82

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire	Eire
Diphtheria	0	0		0	0	*0*	0	*0*	0	0
Dysentery	0	0		0			1		0	
Encephalitis, acute		0			0	*0*				0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	9	0	1	0	2	*9*		*3*	1	0
Influenza	7	0		0	0	*6*	1	*0*	0	0
Measles		0		0	0		0	*0*	0	0
Meningococcal infection		0					1	*0*		
Pneumonia	142	17		4	2	*109*	16		5	6
Poliomyelitis, acute	7	2			0	*7*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis:										
Respiratory	92	13	9	3	2	*113*	15	*21*	4	8
Non-respiratory		0	1	0	0		2	*6*	1	2
Whooping-cough	3	1		0	0	*1*	0	*0*	0	0
Deaths 0–1 year	211	22	25	8	20	*163*	22	*31*	7	11
Deaths (excluding stillbirths)	4,673	660	508	97	136	*3,996*	650	*550*	87	140
LIVE BIRTHS	7,816	1142	915	232	429	*7,039*	1151	*797*	201	413
STILLBIRTHS	176	27	25			*184*	24	*34*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

First Steps to a National Science Centre.—At its meeting on October 7 the London County Council decided to reserve a five-acre site on South Bank immediately east of Waterloo Bridge for the erection of a science centre by the Government. It is intended that the centre should become the home of learned societies, the Patent Office, and the Department for Scientific and Industrial Research. The site is part of the Princes Meadows Estate, formerly an outlying property of the Manor of Kennington which once belonged to the Black Prince.

European Health Community.—The French Government has decided to invite the member-nations of the O.E.E.C. (Organization for European Economic Co-operation) to meet in Paris in December to discuss proposals for the establishment of a European Health Community. The French Minister of Health, M. Ribeyre, asked at a recent Press luncheon how he justified the new Health Community when there was already a World Health Organization, is reported as having pointed to the advantages of co-operation between nations with similar medical problems.

Belgian Prize for Sleeping Sickness Cure.—The Belgian Government is offering a prize of 1,000,000 francs (over £7,000) for the discovery of a cure for sleeping sickness, the late stage of African trypanosomiasis. The prize is open to workers of any nationality. A special jury of three distinguished Belgian doctors, presided over by the President of the Institut pour la Recherche Scientifique en Afrique Centrale, has been appointed to report to the Belgian Minister for Colonial Affairs on any cures submitted to it.

Medical Representation on King George VI Fund.—Among the members of the Philanthropic Scheme Subcommittee of the George VI Memorial Fund, whose composition was announced recently, are several representatives of the medical profession. They are the Presidents of the three Royal Colleges and Dr. Frank Howitt, physician with charge of physical medicine at the Middlesex Hospital. Dr. Howitt is honorary adviser in rehabilitation to the Minister of Labour and a Director of Remploy, Ltd.

Archbishop of York on Spiritual Healing.—In his presidential address to the Convocation of York on October 15, the Archbishop of York, the Most Rev. C. F. Garbett, D.D., spoke on "The Ministry of Healing." In the course of his address he drew attention to the "grave objection to public missions of healing, where preparation of individuals is impossible and where hands are laid indiscriminately upon all who come to them. . . . Without prayer and preparation the laying on of hands and anointing may come dangerously near magic." The Archbishop ended by welcoming the increasing co-operation between the clergy and doctors.

New Safety Precautions at Broadmoor.—The Minister of Health told the House of Commons last week what measures have been taken at Broadmoor to prevent a repetition of the Straffen episode. The measures include the installation of an alarm siren and direct telephone communication with Wokingham police station. New locks have been fitted on the outer doors, and work on re-locking the inner doors is well advanced. A distinctive cloth is to be used for working overalls. In addition emergency plans have been agreed with the police, and discussions are in progress with school authorities and the B.B.C. The security rules are being tightened up, and better pay has been offered to the staff.

Magistrates on Whipping.—At the annual meeting of the Magistrates' Association last week a resolution in favour of the reintroduction of whipping was defeated by 219 to 166 votes. An amendment to the resolution drew attention to the decrease, since the abolition of corporal punishment, in the crimes for which previously it could be ordered.

Dr. H. N. Robson, senior lecturer in medicine at Aberdeen University, has been appointed to the Chair of Medicine at Adelaide University, South Australia. Dr. Robson graduated at Edinburgh in 1941, and has since published papers on disorders of the blood.

Dr. J. C. Broom, deputy director of the Wellcome Laboratories of Tropical Medicine, is going to Washington in December to read the opening paper at a symposium on leptospirosis organized by the U.S. Army Medical Services Graduate School. He will preside at one of the sessions.

Dr. Charles Porter, a former medical officer of health and lecturer on public health at the London School of Hygiene and Tropical Medicine, has been installed as Master of the Plumbers' Company.

NEW ISSUES

Archives of Disease in Childhood.—The next issue of this journal (Vol. 27, No. 135) will be available in a week's time. The principal contents include:

IDIOPATHIC RENAL ACIDOSIS IN INFANCY. S. A. Doxiadis.
CYSTINOSIS: A CLINICO-PATHOLOGICAL STUDY OF TWO SIBLINGS. R. J. K. Brown.
THE TRANSFER OF SODIUM TO THE EXTRACELLULAR SPACE AND CEREBROSPINAL FLUID IN A NEWBORN INFANT. L. Woodrow Cox, T. A. Chalmers, and O. Conor Ward.
AURICULAR FLUTTER IN A NEWBORN BABY. Muriel M. McLean.
COLLODION SKIN IN THE NEONATE DUE TO LAMELLAR ICHTHYOSIS. H. V. L. Finlay and J. P. Bound.
THE SIGNIFICANCE OF YELLOW VERNIX IN THE NEWBORN. W. C. Taylor, J. A. James, and J. L. Henderson.
INITIAL WEIGHT-LOSS. A PRELIMINARY INQUIRY. F. Charlotte Naish.
RATE OF GAIN AND SATIETY IN EARLY INFANCY. Ian G. Wickes.
GASTRO-ENTERITIS IN INFANCY. AN ACCOUNT OF 286 CASES TREATED IN A GENERAL PAEDIATRIC HOSPITAL. N. M. Mann, Sheila Ross, and W. H. Paterson.
ENCEPHALOPATHY FOLLOWING INFANTILE GASTRO-ENTERITIS. L. Crome.
S. TYPHI-MURIUM MENINGITIS OCCURRING IN A PREMATURE INFANT DURING THE NEONATAL PERIOD. V. W. Pugh and S. Vakil.
ATHETOSIS. A STUDY OF 63 CASES, WITH SPECIAL REFERENCE TO HEARING DEFECTS. Patria Asher.
LIPOMA OF THE CORPUS CALLOSUM. W. H. P. Cant and R. Astley.
THE SCHOENLEIN-HENOCH SYNDROME IN CHILDHOOD, WITH PARTICULAR REFERENCE TO THE OCCURRENCE OF NEPHRITIS. M. G. Philpott.
VACCINIA GANGRENOSA. THE REPORT OF A CASE OF PROLONGED GENERALIZED VACCINIA. Bernard Laurance, A. C. Cunliffe, and J. A. Dudgeon.
MORQUIO'S DISEASE. A REVIEW OF THE LITERATURE, WITH A DESCRIPTION OF FOUR CASES. J. D. Whiteside and J. A. Cholmeley.
ENURESIS: A BRIEF REVIEW, A TENTATIVE THEORY, AND A SUGGESTION OF TREATMENT. R. Sessions Hodge and H. M. Hutchings.

Issued six times a year; annual subscription £3 3s., single copy 12s. 6d. Obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

COMING EVENTS

Institute of Urology Lectures.—The Institute of Urology has arranged a series of postgraduate lectures to be given during the next two months at St. Paul's Hospital, Endell Street, London, W.C.2. The lectures will all be at 4.30 for 5 p.m., and the dates, subjects, and speakers are as follows: October 29, Non-tuberculosis Infections of the Renal Tract (Mr. A. C. Morson); November 5, Urological Problems during Pregnancy (Mr. H. G. Hanley); November 12, Prostatic Cancer (Mr. J. D. Ferguson); November 19, Urological Emergencies in General Practice (Mr. J. Sandrey); November 26, Frequency and Other Disturbances of Micturition (Mr. H. P. Winsbury-White); December 3, Indications for Treatment in Enlarged Prostate (Mr. J. F. Barrington); December 10, Diminished Fertility in the Male (Mr. A. R. C. Higham); and December 17, Retention of Urine in Childhood (Mr. D. I. Williams). There is no charge for attendance at these lectures.

Medical Women's Federation Congress.—A special congress of the Medical Women's Federation is being held in London on November 1 and 2 to celebrate the 35th anniversary of its foundation. The opening ceremony will be performed by the Duchess of Northumberland in the Great Hall of B.M.A. House, Tavistock Square, London, W.C.1, at 10.30 a.m. on November 1, after which Dame Hilda Lloyd will deliver the Christine Murrell Memorial lecture, her subject being "Domiciliary Midwifery." In the afternoon there will be a discussion on "The Care of the Child in the National Health Service." On November 2 there will be clinical demonstrations at various London hospitals. The fee for the Congress is 10s. 6d. Further information may be obtained from the secretary of the Federation, Tavistock House North, Tavistock Square, London, W.C.1.

Victor Horsley Memorial Lecture.—The Victor Horsley Memorial Fund, which was raised in 1920 to commemorate the services of Sir Victor Horsley to Science and the Empire, is devoted to the giving of a lecture triennially in London, entitled the Victor Horsley Memorial Lecture. By invitation of the trustees the ninth lecture will be delivered by Sir James Learmonth in the Old Library, B.M.A. House, Tavistock Square, London, W.C.1, on December 11 at 5 p.m. His subject is "Ischaemia in Surgery." Mr. Julian Taylor will be in the chair, and admission is free on presentation of a visiting-card.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 27

MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Medical School, University of Manchester, 9 p.m., "*Opportunities for Research in General Practice*," by Professor Robert Platt.
MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, W.—8.30 p.m., "*The Perils of Blood Transfusion*," discussion to be introduced by Drs. H. F. Brewer and A. E. Mourant.
OXFORD UNIVERSITY.—At Physiology and Biochemistry Lecture Theatre, Oxford University, 12 noon, "*Vitamin B_{12} and Folic Acid*," by Professor A. D. Welch (Western Reserve University, U.S.A.); at Radcliffe Infirmary, Oxford, 2.30 p.m., "*The Biological and Clinical Significance of Intracellular Parasitism in Brucellosis*," by Dr. Wesley Spink (University of Minnesota).
UNIVERSITY COLLEGE, Physiology Theatre, Gower Street, London, W.C.—4.45 p.m., "*Ionization and Biological Activity*," by Professor Adrien Albert (Australian National University).

Tuesday, October 28

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Collagen*," by Dr. E. J. Moynahan.
MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Medical School, University of Manchester, 4.30 p.m., "*Fractures and Fracture-surgeons*," university lecture on the History of Medicine by Mr. D. Lloyd Griffiths.
ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—3.45 p.m., "*Tumours of the Uterus*," Erasmus Wilson Demonstration by Mr. R. M. Haines.
ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5 p.m., "*Epiphora: Its Differential Diagnosis and Treatment*," by Mr. T. M. Tyrrell.
WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—5.30 p.m., "*The Treatment of Subarachnoid Haemorrhage*," by Mr. G. C. Knight.

Wednesday, October 29

CAMBRIDGE MEDICAL SOCIETY.—At Addenbrooke's Hospital, Cambridge, 8.15 p.m., "*Plastic Surgery*," by Mr. L. Rouillard.
GLASGOW UNIVERSITY: DEPARTMENT OF OPHTHALMOLOGY.—8 p.m., "*Prognosis and Orthoptics*," by Dr. A. A. Douglas.
●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Mycology—Tinea Infections*," (1) by Dr. R. W. Riddell.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Chelsea Hospital for Women, Dovehouse Street, London, S.W., 4.30 p.m., "*Conservatism in Gynaecology*," Guest Lecture by Mr. Victor Bonney.
●LONDON MARRIAGE GUIDANCE COUNCIL, 78, Duke Street, Grosvenor Square, W.—6.30 p.m., "*The Medical Aspects of Marriage Preparation*," by Dr. P. M. Bloom.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., "*Disturbances of Hypothalamic Function in Man*," Litchfield Lecture by Professor Dorothy Russell.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—8 p.m., clinical society meeting. *"Principles of Cortisone Therapy in Ocular Disease,"* by Dr. Norman Ashton.

Thursday, October 30

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, W.C., 5.30 p.m., *"Biophysical Studies of Connective Tissue,"* by Professor J. T. Randall, D.Sc., F.R.S.

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, 5 p.m., *"The Clinical and Cytological Investigation of Pleural Effusion,"* by Dr. R. F. Robertson.

●INSTITUTE OF DERMATOLOGY.—Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Mycology—Tinea Infections,"* (2) by Dr. R. W. Riddell.

OXFORD UNIVERSITY.—At Nuffield Orthopaedic Centre, Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., *"The Significance of the Anatomical Findings in Open Operations in Congenital Dislocation of the Hip,"* by Sir Harry Platt (University of Manchester).

RENAL ASSOCIATION.—At Ciba Foundation, 41, Portland Place, London, W., 4.30 p.m., 11th general meeting.

ROYAL ARMY MEDICAL COLLEGE.—At Lecture Theatre, John Islip Street, London, S.W., 5 p.m., *"Korean Experiences"* (with lantern slides and films), by Major J. A. Adam, R.A.M.C.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5 p.m., *"William Cheselden—and the Separation of the Barbers from the Surgeons,"* Thomas Vicary Lecture by Mr. V. Zachary Cope.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5.30 p.m., *"Differential Diagnosis of Proptosis,"* by Miss M. Savory.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, 5 p.m., *"Some Problems of Gastric Secretion of Hydrochloric Acid,"* by Dr. W. I. Card.

●WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At South Kensington Hotel, 41, Queen's Gate Terrace, S.W., 7.30 for 7.45 p.m., dinner meeting and Presidential Address. *"Some Cardiological Misconceptions."*

Friday, October 31

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Scleroderma and Dermatomyositis,"* clinical demonstration by Dr. E. J. Moynahan.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W.C.—4.30 p.m., *"Nasopharyngeal Tumours,"* by Mr. G. H. Howells.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—5 p.m., *"Normal and Pathological Physiology of the Cerebrospinal Fluid Circulation,"* Guest Lecture by Professor G. Schaltenbrand (Würzburg).

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, Ducane Road, London, W., 3 p.m., *"The Thyroid in Pregnancy,"* Guest Lecture by Dr. Russell Fraser.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, London, W.—7.30 p.m., general meeting. *"The Clinical Aspects of Bejel,"* by Dr. G. W. Czonka. Discussion to follow.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5.30 p.m., *"The Physiology of Lacrimal Secretion,"* by Dr. C. A. Keele.

ROYAL INSTITUTE OF PHILOSOPHY.—At University Hall, 14, Gordon Square, London, W.C., 5.15 p.m., *"Mind and Its Place in Nature,"* Manson Lecture by Dr. Macdonald Critchley.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—8 p.m., *"Suicide,"* by Dr. A. Stevenson.

Saturday, November 1

MIDLAND TUBERCULOSIS SOCIETY.—At Chest Clinic, 151, Great Charles Street, Birmingham, *"Radiological Aspects of Congenital Heart Disease,"* by Dr. Peter Kerley.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Happel.—On October 12, 1952, at the Royal Hampshire County Hospital, to Margaret, wife of Dr. John S. Happel, of Ropley, Hants, a daughter—Alison Jean.

Paul.—On October 15, 1952, at the Elizabeth Garrett Anderson Hospital (Hampstead Branch), London, N.W., to Joyce, wife of Dr. Jack Paul, a daughter.

Teasdale.—On October 17, 1952, at the Weir Maternity Hospital, Balham, London, S.W., to Elizabeth (formerly Edwards), wife of Derek H. Teasdale, F.R.C.S., of Wimbledon, London, S.W., a son.

MARRIAGES

Rooney—Brown.—On October 9, 1952, at St. Mary's Church, Hartlepool, Gerard I. Rooney, M.B., Ch.B., to Dora Brown, S.R.N., S.C.M.

DEATHS

Clayton.—On October 4, 1952, at Byron Bay, New South Wales, Australia, Cyril James Weston Clayton, M.R.C.S., L.R.C.P., aged 64.

Graves.—On October 9, 1952, William Ernest Graves, L.R.C.P.&S.Ed., L.R.F.P.S.Glas., late of Bromley Road, Catford, London, S.E., and Rondebosch, South Africa.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Mass Dental Extraction

Q.—*How many teeth should be removed at a sitting when clearing a mouth for a plate? What are the special risks of removing large numbers at a time?*

A.—The number of teeth which should be removed at a sitting depends upon several factors, of which the most important are the health of the patient, the local condition of the teeth and adjoining tissues, and the facilities for after-care of the patient.

The special risks of removing large numbers of teeth at one time arise from infection, haemorrhage, or shock. When infected teeth are removed organisms gain access into the blood stream, and the extent of the bacteriaemia is related to the length of operation and the number of teeth removed. In a healthy individual the bacteria are usually quickly destroyed, but a damaged heart valve, and possibly other sites, may become infected. These dangers can be reduced by limiting the extent and duration of the operation and giving an adequate course of antibiotics both before and after it. Patients with an undue tendency to bleeding should usually have a blood examination. If admission to a hospital is found to be unnecessary extraction of teeth can then be carried out one or two at a time. The risk of infection and haemorrhage can also be greatly reduced by rendering the mouth as hygienic as possible before extraction, by means of scaling and mouth washes, and this should always be done in cases which are not urgent. If superficial infection has been dealt with in this way, six to eight teeth of medium difficulty would be a reasonable number to remove at one sitting for a normal individual who is returning home after a period of rest. More than this should not usually be extracted at one time unless the patient is treated as an in-patient.

A further risk of removing a large number of teeth at one sitting is that the throat pack may become saturated with blood and no longer protect the lungs from the inhalation of septic material.

Urine Alcohol Estimation

Q.—*(1) Is an examination of the urine for alcohol a satisfactory alternative to a blood-alcohol estimation? How should the results be interpreted and what precautions are necessary to obtain a reliable reading? (2) Do any drugs, such as antihistamines, interfere with the estimation of alcohol in blood or urine?*

A.—(1) Examination of the urine for alcohol is in every way as satisfactory as that of the blood, except for the fact that the blood-alcohol figure represents the exact figure at the time of taking, while the urine figure will represent a period earlier. This can be obviated by taking two samples of urine, the first on arrival at the police station and the second after an interval of time has elapsed. Ideally the best course is to take a specimen both of blood and of urine. The interpretation of the result is at the present moment limited to an indication of the minimum quantity of alcohol consumed and absorbed in terms of volumes of spirits, wines, or beers according to their strength. This is then presented in evidence together with the result of the clinical examination (which includes exclusion of the presence of disease which could simulate the effect of alcohol) and a report of behaviour. In the present state of knowledge it is unwise for the prosecution to express an opinion of effect based upon the blood and/or urine figures alone.

The precautions necessary to obtain a reliable result when estimating the concentration of alcohol in the urine may be summarized as follows: chemical cleanliness of the container and stopper; and rapidity of delivery at the laboratory after collection, or, if this is not possible, care of the specimen in order to avoid growth of bacteria. In the case of a blood specimen the following precautions are necessary: avoidance of the use of alcohol or similar substances in the cleaning of the skin; chemical cleanliness of the syringe or container, and absolute exclusion of any alcohol or similar substance in the process; rapid delivery to the laboratory.

(2) No.

Shining Eyes and Lion Men

Q.—*If an animal's eyes are caught in a beam of light at night they are reflected as a red, green, or yellow glow, varying with the kind of animal. Is this the "red reflex" from the retina, and, if so, why do human eyes not normally show this phenomenon? I have recently seen, on three or four occasions, the eyes of an African reflected from the headlights of my car as twin red points. No European I have questioned has ever seen this, but the Africans are very frightened of these men, believing them to be the "lion men" of Nyasaland, and capable of turning themselves into lions or other wild animals. Could this effect be produced by some native herbal drug containing atropine or other such mydriatic?*

A.—A number of factors contribute to the brightness and colour of the light reflected by an eye. Probably one of first importance, as your correspondent suggests, is the diameter of the pupil, or, to be more precise, the ratio of pupil diameter to focal length. This is what photographers refer to as the "F" value of the aperture of a camera lens. Thus F=4 indicates that the diameter of the iris diaphragm is one-quarter the focal length of the lens. The F value is proportional to the square of the required exposure, so that F8 requires four times the exposure of F4. If, then, the ratio of pupil diameter to focal length (say F=4) was, in the case of the eye of a man, twice that of an animal (say F=2) under twilight conditions, the image produced on the animal's retina would be four times brighter than that produced on the human retina. Now similar reasoning applies to the exit beam from the eye: in consequence a uniformly illuminated retina would send out four times as much light at F=2 as it does at F=4. We conclude, other things being equal, that a doubling of the diameter of the pupil increases the brightness of the retinal image four times and the brightness of the emergent beam sixteen times. Now in some animals' eyes—for example, cats—the ratio is often F=1 at night, whereas in man it is seldom larger than F=2; in consequence the cat is more likely than man to produce a bright reflex beam in the headlamp beam from a car. But there are other factors to be taken into account, and one of these is the reflecting power of the retina and of the structures which lie behind it. In many animals—for example, the cat—there is a layer of pigment behind the retina which has a bright surface, called the tapetum, which reflects light strongly. Not only is the retina illuminated by light which reaches it through the pupil, but also by the same light reflected through it a second time by the tapetum. In man the tapetum is absent.

The aberrations of the lens system of the eye also play an important part in determining the visibility of the light reflex. Thus, suppose a lens system free from all aberrations, including diffraction, to be forming a sharply focused image on the retina of a point source of white light, then some of the light rays scattered by this brightly illuminated part of the retina will emerge at the pupil and will proceed back along their path to the light source from which they started and none will be visible to an observer placed outside this beam. For these rays to be visible to him either the lens must be put out of focus or aberrations must be introduced intentionally so as to spread the returning beam. The larger the area of retina which receives illumination the wider will be the area over which an observer will see the light reflex. Now aberrations are more likely to be present when the pupil is large than when it is small, and this is a second reason why a large pupil produces advantageous effects.

We have been considering so far some of the factors which concern the light reflex itself; let us now briefly consider the observer, because the conditions in his eyes affect the apparent brightness of the light reflex. The retina should be dark adapted, the pupil should be dilated, and the angle subtended by the observer's eyes and the headlight of the car at the pupil of the reflecting eye should be as small as possible, because unless this is the case an adequate part of the reflected beam may not stimulate the observer's retina. Returning to your correspondent's interesting question, there can be no doubt that a mydriatic applied to the reflecting eye would be advantageous. It would also help, but to a smaller extent, if instilled into the eye of the observer.

Treatment of Undulant Fever

Q.—*What is the best treatment of long-standing undulant fever? Would treatment with an abortus vaccine help? If so, please give details.*

A.—The antibiotics have replaced vaccine therapy in undulant fever. Vaccines were always of doubtful value in this disorder. Aureomycin is probably the antibiotic of choice, though chloramphenicol and terramycin have been used in a limited number of cases with good results. The fever and general symptoms are sometimes relieved by aureomycin within 48 hours. The adult dose is 1 g. every six hours for two or three days till the temperature has become normal, after which the dose can be reduced to 2 g. daily for about a fortnight, the patient being kept in bed during the period of treatment. Relapses may occur, but respond well to further therapy. When relapses are frequent short courses of aureomycin at intervals of a month may control the fever till sufficient resistance has been acquired to overcome the infection.

Is Boxing Safe for Schoolboys?

Q.—*Is boxing a suitable sport for schoolboys? What are its dangers, and what precautions should the medical officer of a large boys' school insist upon?*

A.—Accidents occur in almost every game. The dangers of boxing are fractured bones of the hand, injuries of the face (bruises, cuts, etc.), and concussion. The medical examination on entrance to school will decide if a boy is unfit for some particular form of exercise. If he is fit for football, he is fit for boxing unless he has a deformed hand or arm. A previously fractured skull, which is rare in children, may be a bar to football or boxing. Subsequent illness or injury may alter the decision made on entrance.

Boxing requires supervision and training. Rules to eliminate the untrained from fights should be ruthlessly applied, especially as their only object may be to get a few points for "the house": this may occasionally exclude the outsider who will knock out the captain of boxing. Fights must be supervised by someone who by experience knows when a boy is liable to be injured because of exhaustion or concussion, and that responsible person must have the power to stop the fight. The medical officer will treat all concussed boys and allow them to resume boxing only when he considers the effects have completely disappeared. Even if all sensible precautions are taken, accidents will occur, but an element of risk is one of the attractions of many games and sports.

All communications with regard to editorial business should be addressed to The Editor, British Medical Journal, B.M.A. House, Tavistock Square, London, W.C.1. Telephone: Euston 4499. Telegrams: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
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